Universidade de Aveiro Departamento de Ciências Médicas
Universidade Nova de Lisboa
2018

ILKA MARTINS ROSA

Caracterização de um Coorte nos cuidados primários na região de Aveiro – Portugal

Characterization of a primary care based Cohort in the Aveiro region of Portugal

Universidade de Aveiro Departamento de Ciências Médicas
Universidade Nova de Lisboa
2018

ILKA MARTINS ROSA

Caracterização de um Coorte nos cuidados primários na região de Aveiro – Portugal

Characterization of a primary care based Cohort in the Aveiro region of Portugal

Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Biomedicina, realizada sob a orientação científica da Doutora Odete Abreu Beirão da Cruz e Silva, Professora Auxiliar com Agregação do Departamento de Ciências Médicas da Universidade de Aveiro.

Dedico este trabalho aos meus pais, ao meu avô, ao marido, à filha, à minha Orientadora e aos pacientes

o júri

presidente

Prof. Doutor José Carlos Esteves Duarte Pedro
Professor Catedrático, Universidade de Aveiro

Prof. Doutor Nuno Jorge Carvalho de Sousa
Professor Catedrático, Universidade do Minho

Prof. Doutor Alexandre Valério de Mendonça
Investigador Coordenador, Universidade de Lisboa

Prof. Doutora Odete Abreu Beirão da Cruz e Silva
Professor Auxiliar com Agregação, Universidade de Aveiro

Prof. Doutora Ana Gabriela da Silva Cavaleiro Henriques
Professor Auxiliar Convidada, Universidade de Aveiro

agradecimentos

Quero expressar o meu agradecimento primeiramente aos meus pais Francisco António Ribeiro Rosa, Maria Puresa Martins Rosa, irmãos, cunhadas, sobrinhos, tios e ao meu Avô. Há um oceano que nos separa e mesmo assim não representa a dimensão da saudade que se sente. Do além-mar carrego cá dentro os princípios, os exemplos e a dedicação. Eles se esforçaram, acreditaram no meu potencial e investiram na minha formação. Suportaram a distância para permitir a realização de um dos meus objetivos de vida que era o de fazer o doutoramento.

Desta distância, surgiram no caminho o Carlos e a Íris, a extensão do amor em família e que passaram também a ser objetivos da minha vida. A eles agradeço a paciência, a compreensão pelos momentos que deixei de com eles estar para dedicar-me à construção de cada tijolo dessa casa que hoje se concretiza.

Agradecer ao Professor Eugénio Franco e ao Professor Ivo Castelo Branco.

Da oportunidade de lecionar, eis que conheço a Professora Odete Cruz e Silva a quem devo um especial agradecimento. Ensinou-me a lecionar, a organizar, a perceber, a respeitar e dar usufruto da rica diferença cultural luso brasileira que hoje carrego. Para além da orientação, incentivo e partilha científica, à minha orientadora devo também o meu amadurecimento, enriquecimento e crescimento pessoal.

Agradecer:

- Ao extinto Centro de Biologia Celular e ao Professor Edgar, apesar da pouca oportunidade de convivência, percebi o grande homem que foi e que ainda se faz sentir presente.
- Ao Departamento de Biologia.
- Ao Departamento de Ciências Médicas.
- A todos os colegas de trabalho da Universidade de Aveiro, em especial a Ana Gabriela Henriques.
- À equipa do Laboratório de Neurociências e Sinalização da UA.
- Aos meus alunos.
- À Universidade de Aveiro.
- À Administração Regional de Saúde – Aveiro e a todos que estão representados na pessoa do Diretor Executivo.
- Aos Pacientes.
- A Portugal que me acolheu.

E tudo isto foi em Glória Dele!

palavras-chave

Demência, Depressão, Genotipagem, Polifarmácia, Medicação Potencialmente Inapropriada, Cuidados de Saúde Primários

resumo

Relatórios da Organização Mundial da Saúde indicam que a expectativa de vida está a aumentar. Demência e depressão estão entre as patologias que mais afetam os idosos; uma população frágil, com recursos e fundos limitados. Muitas vezes, o primeiro ponto de contato para estes pacientes é o médico de família nos cuidados de saúde primários. Com isso em mente, o objetivo geral desta tese foi implementar, nos cuidados de saúde primários, testes cognitivos e de depressão previamente validados, de modo a identificar possíveis pacientes em risco de demência e depressão. O estudo também abordou o uso de polifarmácia, bem como o uso de medicação potencialmente inapropriada (PIM) em idosos.

Para realizar a investigação proposta, foi criada uma coorte baseada nos cuidados de saúde primários (pcb-Coorte); compreendendo 568 indivíduos, uma vez considerados os critérios de exclusão. Ao aplicar o 'Clinical Dementia Rating' (CDR), 68 indivíduos (12%) têm uma pontuação de CDR≥1, dos quais 7 com menos de 65 anos de idade. O pcb-Coorte também foi caracterizado para as comorbidades, e correlações significativas com: condições neurológicas, doenças gastrointestinais (GID), respiratórias e osteoarticulares (OA) são evidentes. A genotipagem para a *APOE* foi realizada, e uma correlação com o alelo de risco para demência, ε4, e baixo desempenho cognitivo (CDR≥1) é clara. Subsequentemente os critérios do DSM-5 para transtornos neurocognitivos (NCD) foram aplicados. O grupo de estudo diminui para 286 indivíduos, dos quais 61 exibem NCD-ligeiro (22%) e 36 NCD-major (13%); 10 têm menos de 65 anos de idade. Correlações com condições neurológicas e doenças respiratórias são sustentadas, mas aquelas com o genótipo de risco *APOE* e GID não são.

A depressão também afeta os idosos e no pcb-Coorte, 174 dos 568 tiveram pontuação positiva na GDS (Escala Geriátrica de Depressão) e 282 têm possível depressão, dos quais 74 estão confirmados com um diagnóstico de depressão. Para ambos os grupos de depressão possível e confirmada (174 e 74) as correlações com OA, GID e uma história de depressão, são evidentes, e mantêm-se mesmo quando versões mais curtas da GDS são analisadas.

Os idosos também representam um grupo de risco para uso potencialmente de polifarmácia e PIM. Os critérios de Beers foram aplicados ao pcb-Coorte para indivíduos com mais de 65 anos e 361 indivíduos tinham informações relevantes sobre o uso de medicamentos. Deste grupo de estudo 94.5% apresentam polifarmácia e 47.4% utilizam pelo menos 1 PIM, sendo o grupo principal os Benzodiazepínicos. Claramente isto é uma preocupação, pois o risco para os pacientes é aumentado.

É possível a partir do trabalho realizado propor várias recomendações. Ou seja, monitorizar os indivíduos no ponto primário de atendimento para identificar possíveis casos de demência e depressão que podem ser recomendados para consultas especializadas. Isto talvez pudesse ser feito através da organização de campanhas nos cuidados de saúde primários. O trabalho futuro focar-se-á nestes aspectos com a intenção de contribuir para a qualidade de vida dos idosos.

Key words Dementia, Depression, Genotyping, Polypharmacy, Potentially Inappropiate Medication Use, Primary Care

abstract

European Health reports from the World Health Organization reveal that life expectancy is steadily increasing. Dementia and depression are among the pathologies that most affect the elderly; a frail population, with limited resources and funds. Often the first point of contact for these patients is the family doctor in primary health care settings. With this in mind the overall goal of this thesis was to implement, in a primary health care setting, previously validated cognitive and depression tests, so as to identify putative at risk patients namely for dementia and depression. The study also addressed polypharmacy usage as well as inappropriate polypharmacy medication (PIM) in the elderly.

To carry out the proposed research a primary care based cohort (pcb-Cohort) was set up; comprising 568 individuals once the exclusion criteria are considered. Upon applying the Clinical Dementia Rate (CDR), 68 individuals (12%) have a score of CDR≥1, of these 7 are less than 65 years old. The pcb-Cohort was also scored for comorbidities and significant correlations with: neurological conditions, gastrointestinal disorders (GID), respiratory and osteoarticular (OA) diseases are evident. Genotyping for *APOE* was also carried out, and a correlation with the risk allele for dementia, ε4, and poor CDR scores (CDR≥1) is evident. The DSM-5 criteria for neurocognitive disorders (NCD) were subsequently applied. The study group falls to 286 individuals of who 61 exhibit NCD-mild (22%) and 36 NCD-major (13%); 10 are less than 65 years old. Correlations with neurological conditions and respiratory diseases are sustained but those with GID and APOE genotype are not.

Depression also afflicts the aged and in the pcb-Cohort, 174 of the 568 scored positive in the GDS (Geriatric Depression Scale) and 282 have possible depression, of which 74 are confirmed with a depression diagnosis. For both possible and confirmed depression (174 and 74) correlations were evident with OA, GID and a history of depression, and sustained even when shorter versions of the GDS were analyzed.

The elderly are a risk group for potentially polypharmacy and PIM usage. The Beers criteria were applied to the pcb-Cohort for individuals over 65 years old and 361 individuals have relevant medication usage information. From this study group 94.5% exhibit polypharmacy and 47.4% use at least 1 PIM and the major group is Benzodiazepines. Clearly this is a concern as risk for the patients is increased.

It is possible from the work carried out to propose several recommendations. Namely monitoring individuals at the primary point of care to identify potential cases of dementia and depression that can then be recommended for specialist consultations. This could perhaps be carried out by organizing campaigns at primary health care centres. Future work will focus on these aspects with the intent of contributing to the quality of life in the elderly.

INDEX

TABLES INDEX

FIGURES INDEX

PUBLICATIONS

Rosa IM, Henriques AG, Carvalho L, Oliveira J and da Cruz e Silva OAB (2017). Screening younger individuals in a primary care setting flags putative dementia cases and correlates gastrointestinal diseases with poor cognitive performance. Dementia and Geriatric Cognitive Disorders, 43(1-2):15-28. doi: 10.1159/000452485; http://www.karger.com/DOI/10.1159/000452485.

Rosa IM, Henriques AG, Wiltfang J, da Cruz E Silva OAB (2018). Putative Dementia Cases Fluctuate as a Function of Mini-Mental State Examination Cut-Off Points. Journal of Alzheimer's Disease, 61(1), 157-167doi:10.3233/JAD-170501.

Rosa IM, Henriques AGC, Marote AMFA, Fernandes EF, Cova MAMN, Afreixo VMA and da Cruz e Silva OAB (2013). Cognitive characterization of a pilot study group. Acta Gerontologia Vol.1 No1 p195. http://actasdegerontologia.pt/index.php/Gerontologia/article/view/41/30

Rosa IM, Henriques AG, Cruz e Silva OAB. Cognitive Performance of Primary Care based Cohort using Mini Mental State Examination. CO39. Sinapse 2015;15:99.

Rosa IM, Henriques AG e da Cruz e Silva OAB Caracterização de pacientes hipertensos num coorte com base nos cuidados de saúde primária na região de Aveiro. Rev Port Hipertens e Risco Card 2019;65:6–17.

Correia M, Lopes J, **Rosa IM**, Henriques AG, Delgadillo I, da Cruz e Silva OAB and Nunes A (2016). Identification of metabolic changes in dementia patients using FTIR. Conference: The 1st International Electronic Conference on Metabolomics. Section: Metabolomics in Human Diseases. Submission ID: sciforum-008812.

Correia M, Lopes J, Silva R, **Rosa IM**, Henriques AG, Delgadillo I, et al. FTIR Spectroscopy-A Potential Tool to Identify Metabolic Changes in Dementia. HSOA J Alzheimer's Neurodegenerative Disease 2016.

Lopes J, Correia M, **Rosa IM**, Henriques AG, Delgadillo I, da Cruz e Silva OAB and Nunes A (2016). FTIR and Raman Spectroscopy Applied to Dementia Diagnosis Through Analysis of Biological Fluids. Journal of Alzheimer's Disease, 52(3), 801-812. doi: 10.3233/JAD-151163. http://content.iospress.com/articles/journal-of-alzheimers-disease/jad151163.

ABBREVIATIONS

-2 Log L- log Likelihood Ratio;

AD- Alzheimer's disease;

ADL- Activities of Daily of Living;

AGS- American Geriatric Society;

AIC- Akaike´s Information Criterion;

ALCOHOL- Excessive Alcohol Use;

APA- American Psychiatric Association;

APOE- Apolipoprotein E;

APOE ε2- alleleε2 Apolipoprotein E;

APOE ε3- alleleε3 Apolipoprotein E;

APOE ε4- alleleε4 Apolipoprotein E;

'*ARS*- Administração Regional da Saúde' (Regional Health Administration);

AUC- Area Under the Curve;

BHP- Benign Hyperplasia Prostatic;

BIC- Schwarz´s Bayseian Criterion;

BZ – Benzodiazepines;

CDR- Clinical Dementia Rating;

CDT- Clock Drawing test;

CI- Confidence Interval;

'CNPD- Comissão Naciontal de Proteção de Dados' (National Commission for Data Protection);

COX- Cyclooxygenase;

CrCl- Clearance of Creatinine;

Crammer´s V- Statistical test to association between two qualitative characteristics;

CSF- Cerebrospinal fluid;

CT- Computerized tomography;

CVD – Cardiac and vascular disease;

DEP- Depression;

DLB- Dementia with Lewy bodies

DM- Diabetes mellitus;

DNA- Deoxyribonucleic acid;

DSM-5- Diagnostic and Statistical Manual of Mental Disorders, 5thedition;

DYS- Dyslipidaemia;

EU- European Union;

‘FCT- Fundação para Ciência e Tecnologia (Foundation for Science and Technology);

FTD- Frontotemporal dementia;

FN- False negative;

FP- False positive;

GDS- Geriatric Depression Scale;

GDS-- Individuals with negative GDS;

GDS+- Individuals with positive GDS;

GDS4Lit- Short version of GDS with 4 questions, from previous literature;

GDS4- Short version of GDS with 4 questions, applied to the pcb-Cohort;

GDS5- Short version of GDS with 5 questions, applied to the pcb-Cohort;

GDS6- Short version of GDS with 6 questions, applied to the pcb-Cohort;

GDS7- Short version of GDS with 7 questions, applied to the pcb-Cohort;

GDS8- Short version of GDS with 8 questions, applied to the pcb-Cohort;

GDS15Lit- Geriatric Depression Scale with 15 questions, from previous literature;

GEECD- Grupo de Estudo em Envelhecimento Cerebral e Demência (in english: Study Group on Brain Aging and Dementia);

GID- Gastrointestinal disease;

GP- General practitioners;

GUD- Genitourinary disease;

HDL- High density lipoprotein;

HEMATO- Hematologic disease;

HIV- Human immunodeficiency virus;

HYP- Hypertension arterial;

IADL- Instrumental Activities of Daily Living;

‘INE- Instituto Nacional de Estatística’ (National Institute of Statistics);

KI- Katz Index;

LDL- Low density lipoprotein;

LR- Likelihood ratio;

LUTS- Lower urinary tract symptoms;

MCI- Mild Cognitive Impairment;

mmHg- Millimetre of mercury;

MMSE- Mini Mental State Examination;

NCD-major-- Neurocognitive disorder major

NCD-mild- Neurocognitive disorder mild

NCD-normal- Normal cognitive performance

NEURO- Neuropathologies;

NFT(s)- Neurofibrillary tangle(s);

NINCDS-ADRDA- National Institute for Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association;

NSAID´s – Nonsteroidal anti-inflammatory drugs;

OA- Osteoarticular disease;

ONCO- Oncology disease;

OR- Odds ratio;

pcb-Cohort- Primary care-based cohort;

PD- Parkinson's disease;

PIM- Potentially Inappropriate Medication;

PIM-1- Medication of the Table 1 of Beers criteria;

PIM-2- Medication of the Table 2 of Beers criteria;

PIM-3- Medication of the Table 3 of Beers criteria;

PNV- Predictive negative value;

PPV- Predictive positive value;

PSP- Progressive supranuclear paraparesis;

RESP- Respiratory disease;

SD- Standard deviation;

SIADH- Syndrome of inappropriate antidiuretic hormone secretion;

SNRIs- Serotonin and noradrenalin receptor inhibitors;

SP(s)- Senile plaque(s);

SPSS- Statistical package for the social sciences;

SSRI- Selective serotonin receptor inhibitors;

NRTI´s- Nucleoside/Nucleotide reverse transcriptase inhibitors;

t – Student's –*t*-Test;

TC- Total cholesterol;

TCA-Tricyclic antidepressants;

TN – True negative;

TP – True positive;

VaD- Vascular dementia;

WHO- World Health Organization;

χ2- Chi-square.

CHAPTER 1

Introduction

1.1 Ageing in Portugal and in Baixo Vouga

In recent years there has been a change in the age structure in Portugal, with a notable decrease in the younger population and a growth in the elderly. The ageing process in Portugal is aggravated by the progressive increase in longevity. The elderly, particularly individuals over 75 years old, account for almost half of the population [1].

Based on the national 2011 census (most recent), Portugal has a total population of 10.3 million, of these 9.8 million individuals living in the continent [2]. In Baixo Vouga, for the same period, the population was 390 822 of which 72 045 are over 65 years of age. From the total population in this region, 187 078 are male and 203 744 females.

In 2013, the resident population in Portugal comprised 14.6% young people (up to 14 years old), 65.6% of legal working age (between 15 and 64) and 19.9% of elderly (more than 65 years old) [3]. The proportion of resident population aged 65 years or older was 18,8% [3]. In 2013 the ageing index in Portugal was 136 elderly (residents aged 65 or over per 100 residents under the age of 15), whereas in the Baixo Vouga region, this was 138 elderly people for every 100 younger individuals [3]. In other words, the ageing index in the Aveiro region is marginally higher when compared to the rest of Portugal.

Perspectives for the future are of considerable concern, given that the ageing trend in Portugal conforms to that followed by member countries of the European Union (EU). That is, an increase is anticipated of 0.3% compared with the previous year and an increase of 2.4 % compared with the last 10 years. In recent years, life expectancy in the EU has improved due to better living conditions and improved public health. In addition, Portugal belongs to the EU countries with better life expectancies. In the EU, life expectation is around 80.6 years, whereas in Portugal, it is 81.3 years, placing Portugal among the most aged countries of the European Union [4].

1.2 Normal Ageing

Physiologically we become compromised as a function of age. Ageing can be detected at a cellular, systems or cognitive level. At a cellular level several changes are evident and these have consequences at a clinical level [5]. Ageing affects systems of

the human body, for instance in the cardiovascular system, decreased cardiac contractile capacity, increased collagenolytic and elastolytic activity, as well as decreased smooth muscle tone can be detected. Together this leads to increased peripheral vascular resistance, an increase in isolated systolic hypertension, hypertrophy of the heart chambers, increased susceptibility to atrial fibrillation, decreased cardiac output and increased susceptibility to ischemia and stroke [5]. Many other functions can be compromised, affecting many other organs. In case of the kidney, the following may happen: a reduction in renal mass, a decrease in cortical thickness, a reduction in glomeruli, a decrease in glomerular lobulation, global glomerular and vascular sclerosis, tubular atrophy and fibrosis. Therefore, there is impairment of kidney responsiveness acute ischemia and injury, and can exhibit increased progression leading to chronic kidney disease, and decreased glomerular filtration rate, or creatinine clearance (ClCr) [5]. Ageing is likewise evident in the respiratory system; there is a decline in the elasticity of the bony thorax, loss of muscle mass and weakening of the muscles used for respiration and reduced mechanical capacity, a decrease in alveolar gas exchange surface area and a decrease in central nervous system's responsiveness. About changes in the mucosa of the gastrointestinal tract, with age, there is a reduction in the endogenous protective factors, and an increase in the aggressors. Both are related to changes in the secretion of endogenous substances. All the above mentioned alterations explain the high prevalence of *H. pylori* in older individuals [6]. Perhaps the most readily visible ageing signs of the human body, are those that affect the most extensive human tissue; the skin: in the ageing skin, there is deterioration of the protective layer of the skin, decreased cell turnover, and reduction in the number of keratinocytes and fibroblasts. Therefore, there is diminished cellular repair, increased incidence of dermatitis, infections, and pressure ulcers.

Many other generalized changes occur. Ageing of the immune system predisposes to infection, increases the chance of reactivation of viral and mycobacterial infections and the response to autoimmunity becomes more pronounced [7]. Other changes include depleted iron stores, low response to acute haemorrhage, poor endocrine response, loss of lean body mass (muscle), and decreased thermoregulation [5]. Additionally, ageing causes a decrease in neural

density; there is loss of fibres of the motor, sensory and autonomic systems; decrease of the sympathetic and parasympathetic tone, and baroreceptor dysfunction. Together these alterations compromise homeostasis, postural hypotension, and can be the cause of syncope [7].

Significantly, cognitive deficits can occur with ageing and these are associated with compromised cortical functions. These include reduced cognitive skills, decreased executive capacities and memory loss. Of note, the ability to respond to injury differentiates normal ageing from neurodegenerative disorders [8]. The cortical volume reduction of a typical older individual (65 years old or more) is around 0.5% in most regions, with more pronounced loss in the frontal and temporal lobes. However, patients with Cognitive Impairment or Mild Alzheimer disease have an annual brain atrophy several times higher than that of healthy individuals, and the most affected lobe is usually the temporal lobe [8]. This is further discussed below.

1.3 Diseases Associated with Ageing

Given the physiological changes related to ageing, the ageing process is associated with several disease processes. Among these the most relevant pathologies include cardiac and vascular disease (CVD), Diabetes Mellitus (DM), cancer and neuropathologies [9]. This contrasts with other common causes of death in the past (typically infectious diseases), mainly because there have been improvements in health and working conditions, diet changes, improved vaccination programs, and the development of antibiotics. Consequently there are clinical and public health implications, because CVD leads to more deaths than other causes together [10,11]. In fact, CVD is the number one killer of men and women, in Portugal [3] and in the world [12]. The risk factors for CVD are well known: hypertension (HYP), dyslipidaemia (DYS), DM, smoking, inflammation and abdominal obesity. The optimal preventive factors are defined as; total cholesterol (TC) between 180 and 199 mg/dL, systolic blood pressure between 120 and 139 mmHg, diastolic blood pressure between 80 and 89 mmHg, being a non-smoker and non-diabetic [9,13]. In 2016, an estimated 56.9 million people died worldwide. The 4 main causes are cardiovascular diseases, cancers, diabetes and chronic lung diseases [14]. The second cause of death in Portugal [3] and in the world

[12] is cancer. Cancer is related to multiple biological changes, involving, in particular, deoxyribonucleic acid (DNA) mutations. These mutations result in the deregulation of cell proliferation and differentiation, and the loss of normal cell function. Other changes include abnormal metabolism and hormonal function leading to malignant cell transformations and ultimately cancer [7,15,16].

Many chronic diseases associated with ageing involve factors that can be controlled. Ageing itself is a process that cannot be regulated, but it can be influenced for example, by changes in eating habits. In fact, controlling calorie intake can decrease chronic diseases and the ageing process [9,17–21].

Another significant group of age associated chronic diseases are neurodegenerative disorders and the exacerbation of cognitive decline. There are studies showing that peripheral metabolic deregulation in patients with DM and CVD, accelerates age associated cognitive decline. On the other hand, high levels of omega-3 intake, calorie restriction, normal body mass index (ratio between 20 and 24), high HDL cholesterol/low LDL cholesterol levels and controlled blood pressure are associated with preserved cortical mass [22,23].

It follows that another important public health problem is dementia [24,25]. The *World Alzheimer Report 2016* estimates that in 2015 there were 46.8 million people worldwide living with dementia and this number it expected to reach 131.5 million in 2050 [25]. Alzheimer Europe website shows an estimated 182.526. that the number of individuals with dementia in Portugal in 2012 was This represents 1.71% of the total population of 10.699.333. Therefore in Portugal, the number of individuals with dementia as a percentage of the population is somewhat higher than the EU average of 1.55% [26]. To summarize, as the population ages alongside increasing life expectancy, the number of individuals with dementia is also increasing.

1.4 Dementia

1.4.1 Prevalence

The global dementia prevalence in 2010 was estimated at 4.7% in people over 60 years old. The region with the highest prevalence worldwide is Latin America, with 8.48% [27]. These values ranged from 2.6% in Africa to 6.2% in Europe and 6.7% in the

USA [28]. It was estimated that in 2010, 35.6 million individuals lived with dementia worldwide, with numbers expected to almost double every 20 years, to 74.7 million in 2030 and 131.5 million in 2050 [11]. In 2010, 58% of all people with dementia lived in countries with low or middle incomes, this is anticipated to rise to 63% in 2030 and 71% in 2050 [27–29]. Clearly this is of significant economic impact and it follows that individuals should be appropriately diagnosed with dementia.

1.4.2 Definition and Diagnosis

Dementia is defined as alterations in memory and other cognitive capacities [30]. The new clinical definition of dementia conforms to that published in the DSM–5 (Diagnostic and Statistical Manual of Mental Disorders, 5thedition) [31]. The manual suggests that dementia is interpreted as a major neurocognitive disorder (NCD-major). For cases of NCD-major there has to be evidence of a significant cognitive decline from the previous level of performance in one or more of the following cognitive domains (complex attention, executive function, learning and memory, language, perceptual ability and motor or social cognition), as perceived by the patient or informant [28,30,32,33]. This is established through standardized neuropsychological tests. NCD-major states that the deficits must interfere with the independent activities of daily living (IADL), that these are not due to delirium, or that the cognitive deficits are not due to any other mental disorder (i.e. depression, schizophrenia) [31,34,35].

Table 1 details the new DSM–5 criteria for neurocognitive disorders [31] [36,37]. To summarize, alterations in at least one cognitive domain must be present, as recognized by the clinician, close observer or by the patient himself, objectified by clinical tests and by a change in the performance of the IADL, excluding (as mentioned above) delirium, major depression and schizophrenia.

Table 1 Criteria for neurocognitive disorders according to the DSM–5

DSM-5 Criteria for neurocognitive disorders
A. Evidence of significant cognitive decline compared to previous performance in one or more of the following domains (complex attention, executive function, learning and memory, language, perceptual, motor, ability or social cognition) based on: 1. Concern of; the individual, acknowledgeable informant, or a clinician, that can confirm that there has been a significant decline in cognitive function; and
B. A substantial deficit on cognitive performance, preferably documented by standardized neuropsychological or quantitative tests, in the absence of the latter another quantified clinical assessment.
C. Cognitive deficits that interfere in the performance of independent daily life activities (i.e., it is necessary help in complex daily life instrumental activities, such as paying bills or managing medication).
D. Cognitive deficits do not occur exclusively in the context of a delirium.
E. Cognitive deficits are not accounted for by another mental disorder (e.g., major depressive disorder, schizophrenia).

Taken from DSM–5 [31].

The DSM-5 differentiates between major neurocognitive disorder (NCD-major) and mild neurocognitive disorder (NCD-mild) [31,38–41]. In NCD-mild, the cognitive decline is modest, and it does not interfere with carrying IADL. Therefore, the term MCI is being substituted by the term mild neurocognitive disorder (NCD-mild).

The term MCI was initially proposed in 1999 by Peterson [42]. A change in cognition, in comparison to the person's previous cognitive level was noted [43]. In this case, the deficits do not interfere with the independent realization of complex life activities. It is still necessary that such deficits are not associated with delirium or other psychiatric disorders [31,42].

MCI/NCD-mild although controversial, is an important stage because many patients classified as MCI/ NCD-mild can convert to dementia, mainly AD [41,43]. It is a disorder/condition of uncertain etiology. Some studies have found increased neuritic plaques in the neocortex as well as cerebral infarction and deposition of Lewy bodies [44,45]. Other studies showed increased acetylcholinesterase activity in the hippocampus of patients with MCI/NCD-mild [46]. To complicate matters further, treatable causes of dementia can occur. These include Vitamin B12 and folate deficiency, hypothyroidism, depression, infectious disease, normal pressure hydrocephalus, tumours, subdural hematoma, drug intoxication, alcohol abuse, kidney/liver/pulmonary/adrenal insufficiency and vasculitis [28,30,47–49].

Dementia diagnosis entails recording the patient's complete medical history, followed by a physical examination, including a neurological examination. It is also necessary to apply cognitive tests or neuropsychological tests. The next step is to request complementary means of diagnosis, such as blood count, biochemical, serological and imaging tests. Currently, including the evaluation biomarkers from blood or cerebrospinal fluid is already contemplated, such as to obtain a reliable diagnosis and promote differential dementia diagnosis [33,35,50–53].

Extracellular amyloid containing senile plaques (rich in the Aβ peptide) and intracellular neurofibrillary tangles (rich in phosphorylated TAU) are considered the central histopathological AD features, and, as such, they represent natural biomarkers [54–57]. It follows that monitoring levels of this triplet (Aβ, total TAU and phosphorylated TAU) provide useful diagnostic tools. Aβ peptides, total TAU and phosphorylated TAU levels can all be quantified in the cerebrospinal fluid (CSF) and provide excellent complementary diagnostic tools. Presently studies are focusing on using patient plasma with mild cognitive impairment and AD, as the source for measuring the same triplet, however, positive reliable results have still to be forthcoming [58–60].

1.4.3 Motives of Cognitive Impairment

Dementia can be characterized into subtypes, as depicted in Table 2, taken from Prince et al [61]. The main causes include Alzheimer's disease (AD), Vascular dementia (VaD), Dementia with Lewy bodies (DLB) and Frontotemporal dementia (FTD).

Table 2 Characterization of dementia subtypes

Dementia Subtype	Clinical Characteristics	Neuropathology	Proportion of dementia cases
Alzheimer´s disease (AD)*	Impaired memory, apathy and depression gradual onset	Cortical amyloid plaques and neurofibrillary tangles	50-75%
Vascular dementia (Vada)*	Similar to AD, but memory less affected, and mood fluctuations more prominent Physical frailty Stepwise onset	Cerebrovascular disease Single infarcts in critical regions, or more diffuse multi-infarct disease	20-30%
Dementia with Lewy Bodies (DLB)	Marked fluctuation in cognitive ability Visual hallucinations Parkinsonism (tremor and rigidity	Cortical Lewy bodies (alpha –synuclein)	< 5%
Frontotemporal dementia (FTD)	Personality changes Mood changes Disinhibition Language difficulties	No single pathology – damage limited to frontal and temporal lobes	5-10%

Table taken from Prince et al [61].

AD is the most common cause of dementia. In 1906, Dr. Alois Alzheimer described this pathology for the first time. The basic physiopathology of this disease, has already mentioned, is the deposition of extracellular neuritic plaques/senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs) within the neuronal brain cells [62]. This is considered the most common dementia subtype (estimates vary from 50-75% or 60-80%) [28].

Several AD risk factors have been described. Higher education levels correlate with decreased incidence and prevalence of dementia of the AD type [63]. Positive correlations with AD have been reported for patients with CVD, hypertension, diabetes, dyslipidaemia, smoking habits and those who are overweight [27,28,62].

At a microscopic and biochemical level, it is consensual that the histopathological changes of AD; namely the SPs and NFTs, lead to neuronal loss and progressive reactive gliosis. Several hypotheses for the development of AD have been proposed (Figure 1), among them the amyloid cascade hypothesis, whereby the toxic peptide Abeta can trigger a series of events. These involve oxidative processes, excitotoxicity, protein aggregation, inflammation and hyper phosphorylation of TAU protein, among others. The result is a deficit in synapses, in neurotransmission and,

consequently, in cognition due to the destruction of the affected anatomical brain regions [64–67].

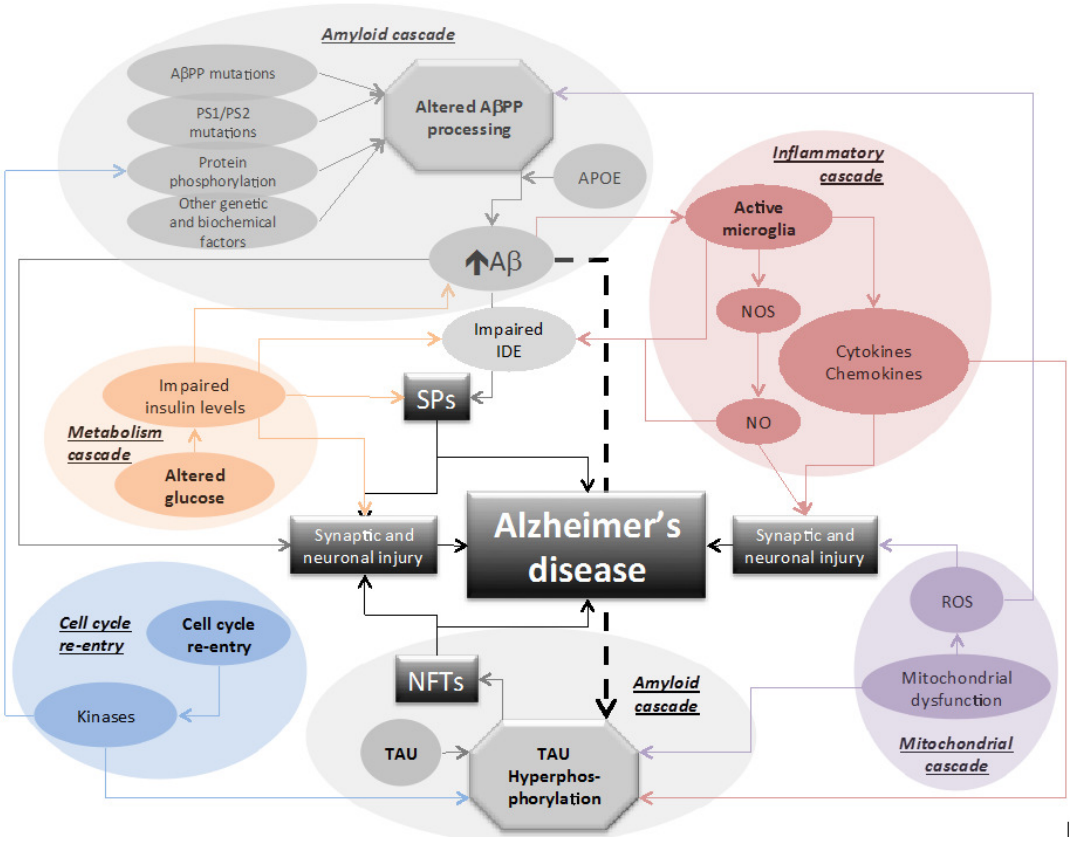


Figure 1 Cascades contributing to the development of Alzheimer's disease

Possible cascades involved in physiopathology of the first cause of dementia; Alzheimer's disease. PS1, Presenilin 1; PS2, Presenilin 2; NOS, nitric oxide synthase expression; NO, nitric oxide; ROS, reactive oxygen species; IDE, insulin degrading enzyme; SPs, senile plaques; NFTs, neurofibrillary tangles. Dashed black line denotes that A can influence tau hyperphosphorylation. Taken from Oliveira et al, 2016 [67].

The second most common cause of all dementias is VaD. In this type of dementia, there is a positive correlation between the onset of cognitive deficits and cerebrovascular events. Patient evaluation includes collecting the clinical history, carrying out a physical examination and analysis neuroimaging tests, as well as scoring for the presence of cerebrovascular disease [28,31]. The latter is a significant risk factor in this pathology. In VaD, the most affected domain is the one related to complex attention and frontal executive functions (planning, decision making, working memory and others). Cognitive decline occurs due to large areas of infarction in cortical regions such as the hippocampus, medial dorsal nucleus of the thalamus,

dorsal or cingulate gyrus. In other words, micro strokes in the cortical area, multiple lacunar infarcts and cortical laminar necrosis are all associated with reduced perfusion and neuronal oxygenation. This typically occurs in patients with CVDs such as hypertension, diabetes or vasculitis [33,68–70].

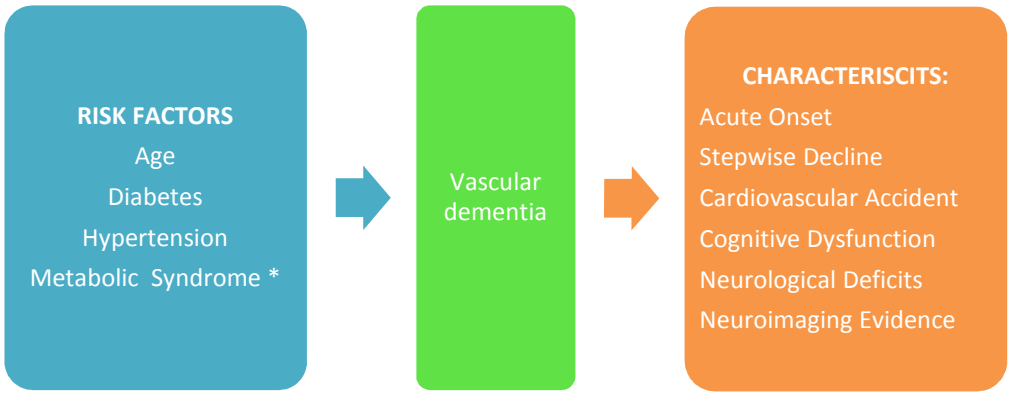


Figure 2 Vascular dementia characterization
Adapted from the risk factors and characteristic features of VaD [70].
*Metabolic syndrome is defined when at least three of the above described findings are present in the clinical evaluation of the patients: *central obesity, hypertension, dyslipidaemia, insulin resistance.*

Dementia with Lewy bodies (DLB) is the third most common cause of neurocognitive disorders and the second cause of neurodegenerative disease is [71,72]. DLB is characterized by the presence of core symptoms that are floating cognition with pronounced variations in attention and waking, recurrent visual hallucinations that are well formed and detailed. Additionally, spontaneous features of Parkinsonism start before the development of cognitive decline [31].

The pathophysiology of DLB has similar mechanisms to those described for Parkinson's disease (PD). Both diseases are characterized by the formation of Lewy bodies and Lewy neuritis' formation. This leads to an abnormal accumulation of the synaptic protein called alpha synuclein. Macroscopically depigmentation of the *substantia nigra* and *corpus coeruleus* can be found, sparing of the cortex and the amygdala can also be detected [33,53,56,57,71,73–75].

Another cause of neurocognitive disorder is Frontotemporal dementia (FTD). The diagnostic criteria include behavioural symptoms: behavioural disinhibition,

apathy or inertia, lack of sympathy or empathy, stereotyped behaviour, hyperorality and change in diet. In addition, in a clinical context, there may also be a prominent decline in cognition and in executive skills. The patient can also exhibit a decline in the ability to speak, in the form of speech production, grammar, choice of words, naming objects or understanding words. In this type of dementia, learning, memory and perceptive-motor function are relatively preserved [76].

Frontotemporal dementias include a set of pathologies that have the same spectrum of clinical changes (progressive deterioration of language and personality changes). Macroscopically, it is possible to see the atrophy of the frontal and temporal lobes. There is FTD with Parkinsonism linked to TAU mutations in brain regions which are affected by atrophic neuronal loss and gliosis due to the presence of TAU containing tangles [77]. In Pick's disease subtype, there is diffuse brain atrophy with asymmetry of the temporal and frontal lobes. Microscopically, cell Pick and Pick corpuscles can be found. In subtype Progressive Supranuclear Palsy (PSP) there is a diffuse neuronal loss of the Globus pallidum, subthalamic nucleus, *substantia nigra*, and colliculus among others. NFTs are found in the affected regions. In corticobasal degeneration, there is a cortical atrophy of the motor cortex, premotor and parietal lobe, with neuronal loss, gliosis, and the presence of neuronal achromasia. In FTD without TAU pathology, the frontal and the temporal lobes are also affected but without TAU deposition, instead the presence of ubiquitin is evident [30,33,77–80].

There are, however, other causes of dementia. PD is associated with dementia but typically in later phases. In other words dementia occurs once PD is installed [81]. Likewise, in Huntington's disease (HD), dementia occurs once the former is already clinically well established. In HD cases dementia can occur earlier if there is a positive family history or positive genetic compliance. Also for Prion disease (Creutzfeldt-Jakob disease) the patient already clinically exhibits the motor characteristics such as myoclonus and ataxia before dementia onset [49].

Furthermore, there are metabolic and endocrine causes of dementia. Examples include: uraemia, Addison's disease; toxins and drug (alcohol, opioids, sedatives) usage; vitamin deficiency (B12, folate, thiamine, nicotinic acid) [49];

autoimmune and inflammatory disorders (systemic lupus erythematosus, vasculitis); and infectious diseases (Human Immunodeficiency Virus, syphilis) [48].

1.4.4 Risk Factors in Dementia

Risk factors for developing cognitive impairment can be modifiable or non-modifiable. Age is undoubtedly a major factor described in many studies and it is considered a non-modifiable risk factor [66,82,83]. Equally non-modifiable is an individual's genotype. The Apolipoprotein E (*APOE*) genotype is considered a risk factor relevant to AD [82], DLB [74]; FTD and PD [53]. Among the acquired and modifiable risk factors, those of vascular origin are of particular concern; obesity, hypertension, diabetes, dyslipidaemia, metabolic syndrome, smoking, high levels of homocysteine, traumatic brain injury [19,22,84].

AD has an unknown etiology, except in familial early onset cases, in which a specific genetic mutation has been assigned. In this scenario, genetic factors appear to be extremely relevant. It is known that a positive family history of AD is the only factor associated with systemic disease, independently of age [85]. AD can be transmitted in an autosomal dominant manner and different genetic subtypes determine the age of onset and evolution. Genetic defects located on chromosomes 14 and 21 are related to early onset forms of AD (below 65 years old). The chromosomes implicated so far in genetic subtypes are chromosome 14 (PSEN1/presenilin 1 gene), 21 (APP gene), 1 (PSEN2/presenilin 2 gene) and 19 (genotypes: *APOE ε4*/ε4, *APOE ε3*/ε3) [86,87]. In the case of genetic testing, there is a significantly stronger association with the *APOE ε4* (allele 4), placing the latter as a risk factor [88].

In Portugal, studies have reported mutations in the presenilin's' coding regions and at exons 16 and 17 of the APP gene, in patients from the Iberian Peninsula with a clinical diagnosis of early AD onset [89]. A person with European ancestry who is homozygous for the alleleε4 (about 2 % of the population) has an increased risk of developing AD, which is three to four times higher than that of an individual of European descent that does not have an alleleε4. Furthermore, the age of onset is likely to be around 10 to 15 years earlier, compared to the sporadic AD age of onset [88,90,91].

Other studies refer that there are protective factors for dementia, which include high education levels (in line with reports for AD, as mentioned above). This is supported by the theory of cognitive reserve, whereby new neuronal pathways are made to compensate for deficits neuronal caused by neuritis [63,92,93]. Again in line with AD, other protective factors appear to be healthy life style habits, such as physical activity and calorie restriction [22,94,95]. As risk factor, to depending on the type of dementia, the association with gender can be variable [82,95–97].

1.4.5 Cognitive Tests

Many tests may be applied in the clinical diagnosis of dementia. In Portugal there is an important manual entitled "Escalas e Testes na Demência (Scales and Tests in Dementia)". This manual is in its third edition and represents the work of several professionals, who over the years have been able to translate and implement the main instruments already validated at an international level, to the situation in Portugal. These questionnaires can, from this manual, be applied to the Portuguese population. It is therefore a work of singular importance for clinical practice and research [98]. Some of these tests and scales are described in more detail below.

The first example, here considered, of a cognitive test is the Clinical Dementia Rating (CDR). The CDR was initially developed and tested for staging dementia in AD patients. This is a semi-structured questionnaire to be applied to both patient and caregiver. It is a screening test for dementia that involves evaluating:

i-memory;

ii-orientation;

iii-judgment and the capacity to resolve problems;

iv-activities in the community;

v-activities at home and the ability to follow hobbies and;

vi-the capacity for personal care.

The first three parameters characterize the cognitive changes. The last three characterize the functional changes. The determinant criterion is memory (i) impairment [99,100]. These parameters (i-vi) can be affected to varying degrees (each

scoring 0-3) and the various combinations permit a CDR score from 0-3 as indicated in Hughes et al and Morris et al [99,100]. The final CDR score is not a simple sum of factors and is explained below.

In CDR, all information relative to the past performance is scored. The disability is considered in relation to the cognitive loss, not in relation to motor abnormalities, depression or personality disorder. In case of doubt, the worst disability is considered. Concerning the scores, CDR 0 means no cognitive impairment; CDR 0.5 questionable dementia; CDR of 1 mild dementia; CDR 2 moderate dementia; CDR 3 severe dementia [100,101]. The conventional CDR is not the simple sum of cognitive parameters. There are guidelines that must be observed. As already mentioned, the traditional scoring considers memory (M) as the primary category (parameter i). All other categories (parameters ii-vi) are secondary (SC-secondary category). The following considerations are observed [99,100]:

- If at least 3 secondary categories (SC) are equal to Memory (M), then the total score is equal to CDR given to Memory evaluation;
- if three or more SC are higher (or<) than the M score, then CDR is equal to most of the SC score that is higher (or<) than the M score;
- when 3 SC have a score on one side of M and the other two SC have a score on the opposite side, then CDR has a score equal to M;
- if M is equal to 0.5 and three or more SC have a score higher than or equal to 1, then the CDR is 1;
- if M is equal to 0.5, CDR cannot be zero; it may only be 0.5 or 1;
- if M is equal to zero, then the CDR is zero unless two or more SC are higher than or equal to 0.5, then the CDR will be 0.5 [100–102].

CDR-Sum Box is the sum of the six cognitive parameters (i-vi) of the CDR. The values range from 0 to 18 points. A sum of 0 is classified as no cognitive impairment. The sum between 0.5 and 4 is the same as questionable cognitive impairment. There is still a subclass in the second step [103–106]:

- the sum between 0.5 and 2.5 is classified as questionable impairment:
- the sum between 3 and 4 classified as very mild dementia;
- the sum between 4.5 and 9 is classified as mild dementia;

- the sum between 9.5 and 15.5 means moderate dementia;
- the sum between 16 and 18 means severe dementia.

Another important cognitive test is the Mini Mental State Examination (MMSE). The MMSE test evaluates orientation, information retention; attention and calculation, evocation and language. It was originally conceived in 1975 [107], and is accepted as a screening test for dementia. It has a maximum score of 30 points. It is divided into two parts. The first section evaluates verbal response on: time orientation (5 points), spatial orientation (5 points), memory (3 points) and attention and calculation (5 points), and memory recall (3 points). This first section has a total of 21 points. The second section evaluates the ability to name objects (2 points), language (1 point), obeying commands (3 points), writing (1 point), reading and executing tasks (1 point), and the ability to copy a complex polygon (1 point). This second section has a maximum of 9 points. In 2009 a study was carried out, evaluating the cognitive performance based on MMSE but took into consideration the educational level of the Portuguese population [108]. Therefore, MMSE was adapted to the Portuguese population.

MMSE is still used today. It has been a valuable tool for dementia screening [42,109], with a sensitivity range between 44 and 100% and a specificity between 46-100% [34,110–113]. It has also been used to evaluate cognitive performance in response to treatments [113,114]. The main disadvantage is related to the second part of the tool, which requires accurate visual capability and writing skills. Therefore, patients with visual problems, low literacy or other language disorders may not be accurately evaluated at a cognitive level [115].

The Clock Drawing Test (CDT) is the third example, here discussed, for cognitive test screening. CDT is considered as good criteria of cognitive screening instrument of dementia and for monitoring cognitive change. It is a good tool to assess motor skills and orientation [116]. It was initially implemented according to the assessment criteria proposed by Shuman [117]. The maximum score results from drawing a perfect clock/watch face (5 points). A score of 4 considers small visual and spatial errors: a slight inaccuracy in the spacing of hours; time drawn outside the circle: turning the

page to write the numbers so that the numbers appear upside down; drawing lines to guide time. A score of 3 refers to an inaccurate representation of the requested time even though, the visual and spatial representation is perfect, or has only minor deviations. A score of 2 refers to minor visual spatial clutter of time, so that the patient cannot indicate the requested time: showing inability to write numbers; drawing the numbers counter clockwise; repeating: the cycle continuing beyond 12, numbering the time as 13, 14, 15 and so on; omitting numbers, keeping a poor space between numbers. A score of 1 refers to severe disruption of those inabilities described for a score of 2. A zero score refers to no attempt at all, drawing something that does not look like a clock/watch or being unable to write numbers, writing a word or a name instead.

The CDT is a widely used test for cognitive evaluation. It is easy to manage and quick to perform [116]. It has a good correlation with MMSE and other cognitive tests [118,119]. Further it is useful for evaluating temporal dementia deterioration [120–122].

There is, however, an arsenal of clinical trials for screening and diagnosing dementia. These include the Montreal Cognitive Assessment (MOCA), the Cambridge Computed Neuropsychological Testing Battery for Dementia Assessment, the Neuropsychiatric Inventory (NPI), among others, many of which can be found in the manual of Dementia Scales and tests for the Portuguese population [98]. In general, these tests evaluate the cognitive domains, and serve as important screening and diagnosing tools that have been internationally validated for use in clinical practice and for research application.

In dementia, it is very important to assess the degree of dependence in patients. Dependence may exist when needing to perform basic activities of daily living (ADL) or instrumental activities of daily living (IADL) . The Katz index (KI) [123,124] is a widely used and validated instrument worldwide to evaluate performance of the ADL. ADL is a very useful tool to detect the patient's skills in taking care of himself or herself, with respect to six functions: bathing, dressing, using the toilet, and controlling sphincters [123]. ADL can be classified into 3 categories: Independence (the patient is completely autonomous), Partial Dependence (the patient is partially dependent, performs activities not properly or with little difficulty) and Complete Dependence (the

patient is unable to perform any activity on his/her own). There is the possibility of 8 different classifications: A- the patient is completely independent; B- the patient is independent in all activities, except in one; C- independent in all the previously mentioned activities, except bathing, and one other function; D- as criterion C, but also dependent with respect to dressing; E- as criterion D, but also dependent with respect to utilization of the toilet; F- as criterion E, but also dependent with respect to mobility; G- dependent for all 6 functions; Other- when there is no classification in C, D , E and F but with dependency on two activities.

The ADL is a frequently used tool in research and by doctors in their daily consultations. This is because ADL helps physicians, caregivers and institutions to establish the patients' needs [123,125–128].

Cognitive decline in instrumental activities of daily living (IADL) is part of the diagnostic criteria for dementia [31], discussed above. There is a correlation between IADL and dementia/AD evaluation [129]. The IADL analyses the skills/capacity and social independence of the patient (ability to use the phone, to do the shopping, to cook, to do the house shores, to take care of clothing, to move, to be responsible for taking medication, to be able to manage his/her own money) [129,130].

It is important to determine whether the patient has or has not changed the performance with respect to instrumental activities. First, according to the DSM-5, it is used to separate the diagnosis of NCD-major (changes in IADL are observed) and NCD-mild (changes in IADL are not observed). Secondly, it allows doctors, family and institutions to plan interventions depending on the degree of disability already reflected by the patient [131–134].

1.5 Depression

Depression and dementia can be confused, as both can show similar signs and symptoms [49,135,136]. Although dementia is widely recognized as a characteristic age related problem, depression is more frequent [137], and a serious problem in the elderly. It reduces the quality of life and it can destabilize medically controlled comorbidities in the elderly. Depression was the most disabling disorder worldwide, measured in the number of years living with this disability [138]. Pooled prevalence

was 17.1% (95% CI 9.7–26.1%) for depressive disorders [139]. Alarmingly in Portugal, a study showed that about 33% of the general population presented depressive symptoms [140,141]. It is evident that improving Depression care quality is urgently needed, furthermore given that cases of depression can go undetected, many cases fail to receive minimally adequate treatment [29]. The frequent occurrence of clinically relevant depressive symptoms should be considered in health care planning [142], particularly at the point of care (primary care healthy).

1.5.1 Definition

Depression comprises a large, heterogeneous group of psychiatric disorders. The DSM-5 criteria for depressive disorders includes the group of pathologies that have as common characteristics the presence of sadness, emptiness, irritable mood, accompanied by somatic and cognitive alterations that significantly affect the capacity to function as an individual. What differs between the various disorders grouped in the depressive disorders are issues related to duration, timing, or presumed etiology. Bipolar Disorders [37] are not considered a subtype of depression, as was done so in DSM-IV. The diagnostic criteria for depression based on the DSM-5 are transcribed below.

Table 3 Criteria for depressive disorders according to the DSM-5

DSM-5 Criteria for Depression
A. Five (or more) of the following symptoms present during the same two week period and represent a change from previous functioning; at least one of these symptoms is (1) depressed mood or (2) loss of interest or pleasure. *1. Depressed mood most of the day, almost every day, as indicated by subjective report (e.g., feels sad, empty, and hopeless) or by observation by other people (e.g., seems tearful). (Note: In children and adolescents, it can be irritable.)* *2. Decreased interest or pleasure in all or almost all activities most of the day, almost every day (indicated by subjective report or observation made by others).* *3. Significant weight loss or gain without dieting (e.g., a change of more than 5% of body weight in a month), or reduced or increased appetite almost every day. (Note: In children, consider failure to achieve expected weight gain.)* *4. Insomnia or hypersomnia almost every day.* *5. Psychomotor agitation or retardation almost every day (observable by other people, not merely subjective feelings of restlessness or being slowed down).* *6. Fatigue or loss of energy almost every day.* *7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) almost every day (not merely self-recrimination or guilt about being ill).* *8. Decreased ability to think or concentrate, or indecision, almost every day (by subjective report or observation made by other people).* *9. Recurrent thoughts of death (not only fear of dying), recurrent suicidal ideation without a specific plan, suicide attempt or specific plan to commit suicide.*
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of life.
C. The episode is not attributable to the physiological effects of a substance or other medical condition.
***Note:** Criteria A-C represent a major depressive episode*
D. The occurrence of a major depressive episode is not better accounted for by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, other schizophrenia spectrum disorders and other specified psychotic disorders, or schizophrenia disorder and other unspecified psychotic disorder.
E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all manic or hypomanic type episodes are substance induced or attributable to the psychological effects of another medical condition. Taken from [36].

The depressive disorders detailed in DSM-5 include disruptive mood disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/drug-induced depressive disorder, depressive disorder due to another medical condition, another specified depressive disorder and unspecified depressive disorder. This tool can be used in various healthcare settings, including the primary point of care.

1.5.2 Causes and Associated Factors in Depression

Depression has been shown to be associated with major life changes and stress, little or no social support, low socioeconomic status often aggravated by increased medical costs, female gender, age and family history of mental illness, chronic physical or mental disorders; leading to increased functional impairment and decreased quality of life [143].

As mentioned, depression is a major health problem in women [144], and in Europe, the disease has a strong association with low educational level and the "not married" status [150]. The relationship between depression and compromised physical condition is also recognized [145]. There is a higher prevalence of major depressive disorder in patients with chronic medical illnesses. There is evidence in the literature that some comorbidities are directly correlated with depression: heart attacks, diabetes mellitus, chronic obstructive pulmonary disease, cancer, PD and pain [146,147]. Depressive symptoms occur in about 15 to 20% of cases following a coronary event [148]. Of note, 20% of patients with cerebral vascular stroke develop depression. The world health organization predicts that by 2020, depression will have outpaced the negative impacts of other diseases such as ischemic coronary disease, neoplasms and CVDs [149]. The pathophysiological explanation is based on the autonomic nervous system imbalance, with over sympathetic activity and low parasympathetic activity, with decreased cardiac rhythm variability, down regulation of beta adrenergic receptors, and decreased sensitivity of baroreceptors, increasing susceptibility to arrhythmias. Autonomic imbalance is an independent risk factor for cardiovascular mortality [150]. Additionally a significant genetic risk factor associated with depression has been identified; namely being an *APOE ε4* carrier [151].

As mentioned there is a strong link between dementia and depression and in fact, post-stroke depression has been associated as a predictor of poor quality of life and risk of cognitive impairment [144]. Many elderly patients with major depressive disorder have cognitive and mood alterations, and memory loss [135]. The prevalence of depression in patients with AD is on average 17%, which may increase in patients with VaD [140]. Depression in PD is associated with increased physical disability, worsening of quality of life, and decreased social interaction [141].

The presence of comorbidities and cognitive alterations are two key factors for consideration in the diagnosis and management of depression [138]. It is well known that cognitive impairment may persist even after treatment for depression. This is probably due to the combined effect of age and depression on changes in the brain; such as atrophy and vascular disease. Some epidemiological studies have shown that depression appears to be a risk factor for cognitive impairment or dementia [152].

1.5.3 Testing for Depression using the Geriatric Depression Scale

It is essential when screening for dementia to also have a test that can correct for depression. It is common a patient has dementia and depressive disorder together. Further confusion can arise as a given patient can exhibit both conditions as comorbidities [27,145,146].

The Geriatric Depression Scale (GDS) was designed for the screening of depression in the geriatric population. Initially 30 items/questions were included [139]. It is a scale translated and adapted for several languages. This version has also been translated for use in Portugal [153]. GDS consists of questions that address personal, family and social factors with dichotomous responses [154–156]. Presently, the GDS with 15 questions (GDS15) is commonly implemented in primary health care situations [157]. The literature shows that GDS15 represents a useful, fast and reliable tool for the screening of depression in adults [156–158]. The questions in the GDS15 are described in table 4.

Table 4 Sample rating GDS15

Geriatric Depression Scale-The questions	
1.	Are you basically satisfied with your life?
2.	Have you dropped many of your activities and interests?
3.	Do you feel that your life is empty?
4.	Do you often get bored?
5.	Are you in good spirits most of the time?
6.	Are you afraid that something bad is going to happen to you?
7.	Do you feel happy most of the time?
8.	Do you often feel helpless?
9.	Do you prefer to stay at home, rather than going out and doing new things?
10.	Do you feel you have more problems with memory than most people?
11.	Do you think it is wonderful to be alive now?
12.	Do you feel pretty worthless the way you are now?
13.	Do you feel full of energy?
14.	Do you feel that your situation is hopeless?
15.	Do you think that most people are better off than you are?

Taken from [158]

The GDS15 can be applied to screen for individuals with Depression. Of note, note all the criteria for Depressive disorders in the DSM-5 are contemplated in the GDS15 questions. Thus, care should be taken in not directly applying the GDS15 as a diagnostic tool. Depression is often encountered at the point of care and there is a heavy burden to appropriately diagnose and medicate these patients. The medication most often used for Depression is discussed in the section below; this is particularly relevance as the family clinician has, only in the last few years, been at liberty to freely medicate (with the participation of the health ministry) for this condition.

1.6 Medication in the Geriatric Population

Polypharmacy and Potentially Inappropriate Medication (PIM) use in elderly patients is an important question that physicians need to be aware of. People over the age of 65 have a higher prevalence of chronic illnesses, disability and dependency than younger counterparts [159]. The elderly often takes several drugs at the same time, to treat concomitant disease processes [160].

1.6.1 Polypharmacy

Polypharmacy is applied in cases involving the use of five or more prescribed drugs [160]. The use of multiple medications, commonly prescribed to the elderly, leads to reduced compliance with drug treatment regimens and increased risk of adverse drug reactions [159]. Further, polymedication increases the risk of prescribing PIMs as well as the occurrence of harmful consequences [159]. Adverse drug reactions and polypharmacy represent major positive associations with morbidity and mortality, and are common among ambulatory geriatric patients and more than a quarter of them were preventable [160]. Additionally, and of relevance, the risk-benefit ratio is often extrapolated from the younger adults to the geriatric population; obviously this is not necessarily valid [161]. Not surprisingly, medication revisions, addressing the older population, resulted in a significant reduction of prescribed drugs (average 0.45 drugs; 95%CI 0.11-0.76) [162]. Likewise, the need to develop and evaluate new strategies to reduce the risk of drug-related incidents in the geriatric patient population became evident [161,163,164]. In this respect, the Beers Criteria has become a significant resource to increase safe care, achieve quality improvement and obtain enhanced patient outcomes [162]. This is further discussed below.

1.6.2 Potentially Inappropriate Medication

In 1991, Dr. Beers and colleagues studied the use of safe and appropriate medications in older adults. This study was developed in patients admitted to a continuo care facility. Potentially Inappropriate Medication (PIM) was defined as the use of potentially inappropriate drugs whose use represents a risk greater than the benefit [161]. The work identified a set of drugs, or group of drugs, whose use may be classified as PIM in the elderly.

The definition of PIM considers the following concepts:

- does the risk outweigh the benefit;
- over-prescribing: excessive dosage and/or duration of medications associated with polypharmacy;
- mis-prescribing: is there an unfavourable choice of medication, dose, or duration;

- under-prescribing: not prescribing a clinically recommended medication, if the patient does not have any contra-indications for using the referred medication [163].

Each of the thirty (original set in 1991) Beers Criteria identifies a drug or class of drugs that are identified as potentially inappropriate and that are part of the ordinary prescription among doctors. They are: sedative-hypnotics, antidepressants, antipsychotics, antihypertensive, nonsteroidal anti-inflammatories, oral hypoglycaemic agents, analgesics, dementia treatments, platelet inhibitors, histamine blockers, antibiotics, decongestants, iron supplements, muscle relaxants, gastrointestinal antispasmodics and antiemetic's. Applying the Beers Criteria is useful for reviewing quality assurance, health services research, and clinical practice guidelines. These criteria can be used to update and expand future guidelines [161].

In essence, the Beers criteria define medications that should generally be avoided in the ambulatory elderly patients, the doses or frequency of administration that should generally not be exceeded, and the medications that should be avoided in older persons who have known clinical conditions [163]. The Beers criteria have been used as a clinical guide.

The Beers Criteria have evolved over time (Table 5). First established in 1991, as described above, in 1997, there was an update of the criteria by the same author. A panel of experts convened to expand the criteria for the elderly, and not only for those institutionalized (as for the 1991 version). This expert panel agreed on the validity of 28 of the original 30 criteria for inappropriate use of medication in the elderly. In addition, this expert panel agreed on 35 additional criteria that define PIMs associated with conditions/diseases of the elderly [162].

Table 5 Temporal evolutions of the Beers Criteria

Year	Criteria
1991	Beers Criteria applied in elderly nursing home [161]
1997	Revised and applied to older adults in the community [163]
2003	Revised to include two categories of PIM [162]: Medications that can be avoided Medication that can be avoided based on the patients' diseases/conditions
2008	Applied Beers Criteria in the Portuguese Population[165]
2012	Revised criteria [166]

In 2003 (Table 5) the Beers Criteria were again updated [162]. The changes were as follows:

1. Reserpine (Reserpine in doses>0.25 mg) was added to the list;

2. The criteria encompassing oxybutynin was altered to include both the extended-release oxybutynin and the immediate-release formulation;

3. Whereas previously all iron supplements>325 mg was considered, in the revision only ferrous sulphate is included;

4. Only the short-acting dipyridamole is considered (Persantine- long-acting dipyridamole is not, which has better properties than the short-acting dipyridamole in older adults except in patients with artificial heart valves).

In 2008, a Portuguese group operationalized the Beers Criteria in Portugal [165]. The study had 193 participants, the prevalence of PIM varied from 24% to 73%. The application of the criteria revealed that a high number of chronic medication usage was a common risk factor to have at least one PIM. Of the 1713 medications reviewed, 5.6-14.8% were considered PIMs [164].

In 2012, Beers Criteria were revised to those used up until 2015. A set of tables (Tables 1-3 of the Beers Criteria) describing the Beers Criteria was developed (see Supplemental Tables 1-3 in annex 1). Table 1 of the Beers Criteria describes the 34 PIMs and classes to avoid in older adults. Notably new additions include megestrol, glyburide, and sliding-scale insulin. Table 2 of the Beers Criteria shows potentially inappropriate medications and classes to avoid in older adults with certain disorders

and syndromes that the drugs listed can exacerbate. The change is that in 2012 there are new additions: thiazolidinediones or glitazones with heart failure, acetylcholinesterase inhibitors with history of syncope, and selective serotonin reuptake inhibitors with falls and fractures. Table 3 of the Beers Criteria indicated the medications that should be avoided or used with caution in patients above 75 years old.

There are however other explicit criteria besides the Beers Criteria to evaluate medication usage. The table below summarizes the more commonly used methods (Table 6).

Table 6 Explicit criteria to evaluate the use of medications

Study (Year)	Explicit Criteria
McLeod (1997)[167]	Canadian Consensus panel list of PIM
Rancourt Criteria (2004) [168]	Developed by geriatrics research team in Canada with four potentially inappropriate categories: medications; duration; dosage; and drug-drug interactions.
Lorache Criteria (2007) [169]	Similar Rancourter Criteria applied in France
STOP/START [170]	STOP criteria to detect PIM and START criteria to detect omission in the prescribing

Of these the STOP/START is the most used. STOP means Screening Tool for Older Persons. These criteria have 65 indicators for PIM that include: interactions, contraindications, therapeutic duplication, medications that increase the risk of falls. These criteria consider various types of therapeutic strategies commonly used in clinical situations, of a cardiovascular, central nervous system, psychotropic, gastrointestinal, respiratory, skeletal muscle and urogenital nature, but also drugs that can induce falls and the use of analgesics.

In addition to these studies, there are many others. The central objective is to apply evidence-based guidelines for avoiding commonly encountered prescribing related problems. In general, these goals are achieved through improving medication appropriateness, preventing adverse drug events and as a final result, reduce drug expenditure [170].

1.6.3 Medicating for Dementia

In the treatment of cognitive deficits, various types of dementias may be underlying the condition. Typical medications include cholinesterase inhibitors; those typically available include donepezil, rivastigmine and galantamine. These substances increase central cholinergic neurotransmission by inhibiting the decomposition of acetylcholine by acetylcholinesterase [88]. However, dementia is typically accompanied by non-cognitive symptoms such as agitation, anxiety and depression. In the treatment of agitation symptoms, conventional and atypical neuroleptics, benzodiazepines, trazodone, and anticonvulsants are effective [171].

The treatment of acute anxiety can be managed with benzodiazepine. However, if the patient continues to present an anxiety disorder for more than 4 weeks, a change is recommended to the antidepressant selective serotonin reuptake inhibitors (SSRIs). This is so because dependence can develop with the chronic use of benzodiazepines [172].

In the treatment of depression, in patients with dementia, serotonin reuptake inhibitors are preferred, since anticholinergic drugs should be avoided. In patients with mood disorders or sub-types, mood stabilizing drugs or their variants may be prescribed, such as lithium or valproic acid [173].

1.6.4 Medicating for Depression

A large range of drugs are available for managing depression: old and new tricyclics, tricyclics atypical antidepressants, reversible and irreversible monoamine oxidase inhibitors, SSRIs, selective serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenaline reuptake inhibitors [174].

Special attention must be paid to interactions and side effects of these drugs. It is important for the clinician to master this subject to avoid inappropriate use of medication in the elderly population. For example: the major metabolic pathway associated with anti-depression drugs involves the enzymes of P450. Through the enzymes route 2C and 3A of this system, SSRI can inhibit the metabolism of benzodiazepines, calcium channel blockers and theophylline. Additionally, citalopram, escitalopram and sertraline should be preferentially indicated in the elderly because

they are the least involved SSRIs in the interactions of P450. The clinician should know that the side effects of tricyclics are due to ant muscarinic effects. This implies dry mouth, blurred vision, constipation, urinary retention and can lead to cardiac arrhythmias, so it is not a drug of choice in the elderly population [175].

In closing it is important to realize that increasingly the elderly require specialized care given their increased risk of dementia, depression and even PIM. Further the elderly is the most vulnerable and financially the frailest sector of society. Often their major means of health care are the primary health care centres. This dissertation considered some these major issues with the intent of being a useful contribution for clinicians at point of care.

CHAPTER 2

Study Framework and Objectives

2.1 Framework

Dementia is widely regarded as a public health problem. The incidence of dementia in Portugal has increased with the ageing of the population. This was not accompanied by a social conscience towards the special needs of the elderly or by a corresponding legal framework. Many elderly individuals with dementia live in isolation or with little family network. In essence they lose their autonomy, and run the risk of seeing their rights, their freedom and even their guarantee as individuals being questioned or violated [24] .

Recognition of dementia at the primary point of care has been confirmed to be low in many studies conducted in high-income countries. Findings show that there is generally no structured program to identify putative dementia cases in a primary care setting and there is no evidence of general practitioner training for diagnosing dementia. This translates into limitations with respect to recognizing this condition in primary care practices [25].

In the Baixo Vouga region of Portugal there is a shortage of studies investigating the elderly, particularly with respect to dementia but also depression at the primary point of care. From a practical viewpoint it is important to compare the various methodologies readily available to identify putative at-risk cases with respect to cognitive impairment and depressive status. To do so, a primary care-based cohort (pcb-Cohort) was established and characterized with respect to cognition and depression in the Aveiro region. It was also possible to collect blood from volunteers, thus genotyping for APOE (a well-established risk factor for Alzheimer's disease) was carried out.

Another essential aspect at the primary point of care is to look at ways of; increasing safe care, achieving quality improvements and obtaining enhanced patient outcomes. Additionally, the elderly is often, due to frail physical conditions, subjected to polypharmacy, thus the Beers Criteria can be used as a significant resource. In this respect the number of Potential Inappropriate Medications (PIMs) and polypharmacy in individuals in the pcb-Cohort were identified.

The data presented is expected to provide a valuable profile of patients 50 years of age or older in the Aveiro region with respect to dementia, depression and

PIM. A 50-year-old cut-off is important to identify putative cases as early as possible and the family physician is in an ideal position to do so. In other words, it is important to identify at risk cases prior to being considered elderly. It is expected that the data produced will be a valuable tool, for family physicians.

2.2 General Goal:

To establish a primary care based cohort (pcb-Cohort) focussing on the primary point of care and to test tools to characterize the functional capacity and the prevalence of dementia and depression in this sub-population, as well as patterns of medication usage in individuals 50 years old or more.

2.3 Specific Objectives:

1. To establish a cohort of individuals based on the primary point of care (pcb-Cohort);
2. To implement a 'pcb-Cohort' of individuals 50 years old or more, in the Baixo Vouga region;
3. To assess the functional ability of the participants in performing Daily Living Activities and Instrumental Activities of Daily Living;
4. To determine the putative dementia and depression prevalence and that of other comorbidities in the population under study;
5. To explore the feasibility of shorter GDS versions (including fewer questions);
6. To genotype the pcb-Cohort for *APOE* (the highest genetic risk factor for Alzheimer's Disease, thus far shown) and to assess any forthcoming correlations with cognitive impairment and other comorbidities;
7. To profile prescription drug usage in the pcb-Cohort;
8. To identify prevalence of polypharmacy and analyse the factors associated with polypharmacy and PIM (Potentially Inappropriate Medication).

CHAPTER 3

Methodology

3.1 Study Design

A cross-sectional population-based survey on a Portuguese volunteer group, in the Aveiro district, was carried out. The intent was to develop a cohort of patients attending primary health care; a primary care based cohort (pcb-Cohort). Prior to initiating the project, approval for the study was sought and obtained from ARS (see annex II). A first consideration when developing a study of the type here presented, is the number of individuals that should be included. The Aveiro district had 78450 habitants in the 2011 CENSUS (in www.ine.pt), and the target size should include at least 480 individuals [176]. The study here presented involved 590 individuals (568 fulfilled the criteria). Of the 22 participants excluded, 9 were less than 50 years old, 12 were aphasic and could not communicate to fill in the questionnaires and 1 did not complete the questionnaire.

As a first step, a meeting was held with representatives of the primary health care centres (Representantes do Agrupamento de Centros de Saúde do Baixo Vouga). The study was presented, and participations were encouraged. Five primary health care centres were randomly chosen. Individuals attending the respective point of care, aged 50 years or older, were invited to participate. Volunteers were extremely willing to participate and readily came forward. Participants, many accompanied, provided written informed consent, individuals unable to give consent were excluded.

The study involved four stages (Figure 3). Participants completed a structured interview covering their respective life history, general health and well-being. Next, cognitive evaluations and dementia screening tests were performed (stage 1). For practical reasons, and to avoid recalling participants, blood was collected during stage 1 (it was used for genotyping, stage 3). In stage 2, the clinical data available from clinical records, including comorbidity information were scored. Participants were genotyped for APOE (stage 3). In stage 4, analyses of the data collected were carried out blind to the data from the other stages. All data collected for each participant were evaluated with the Statistical Package for the Social Sciences (SPSS) [177].

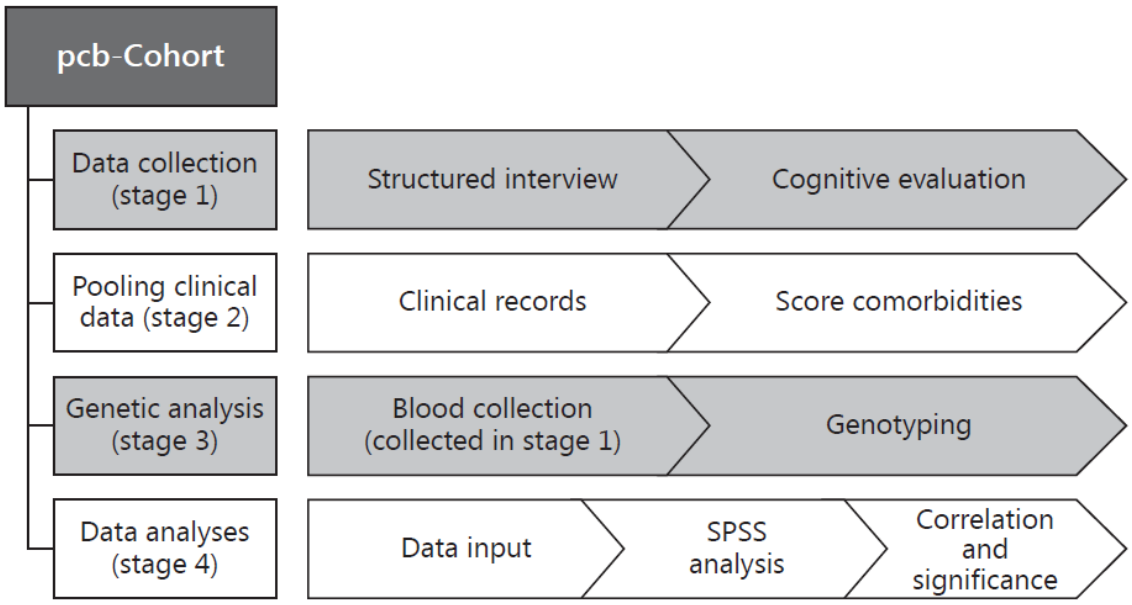


Figure 3 Experimental workflow
Approach used to study the pcb-Cohort. Stage 1: a structured questionnaire was applied to patients 50 years or older in primary care in the Aveiro district, Portugal. Stage 2: cognitive testes were carried out, and information regarding clinical records collected. Stage 3: blood was collected for *APOE* genotyping. Stage 4: data was organized in SPSS; bivariate and multivariate analyses were performed.

3.2 Inclusion and Exclusion Criteria

Volunteers were admitted, independent of complaints or deficits in any cognitive domain. Mandatory inclusion criteria to be 50 years or older was observed. Individuals undergoing oncological treatment, diagnosed with psychiatric disorders (excluding depression), aphasia, or unable to answer the questions in the structured interview were excluded. To ensure generalizability, exclusion criteria were kept to an absolute minimum.

Volunteers meeting the above criteria signed an informed consent, the research was explained, its consequences and the possibility to leave the study at any time were guaranteed, without prejudice to the participant. Confidentiality was assured. The study is part of a project approved by the ethics committee for health of the Central Regional Administration in Coimbra (Comissão de Ética para a Saúde da ARS Centro, protocol 012804-04.04.2012), and by the National Committee for Data Protection.

3.3 Clinical Interview

Data collection for the clinical interview, Stage 1 (Figure 3) initiated with a structured interview and was then followed up by a cognitive evaluation (see annex III). Of the 590 volunteers, 568 fulfilled the inclusion criteria. Participants underwent a semi-structured questionnaire addressing sociodemographic characteristics, personal and family history. Data concerning medication usage was also collected, but this is further discussed below.

For data analyses by the SPSS, participants in the pcb-Cohort were stratified according to age. The following groupings were used: patients from 50 to 64 years old, those from 65 to 74 years of age, and finally patients over 75 years old. Education level was categorized into three groups: less than 2 years of schooling, from 3 to 6 years of schooling, and more than 7 years of schooling. Relative to marital status, subdivisions were: patients living with a partner and other situations. For professional status the following were considered: active, reformed and unemployed. In terms of monthly family income two subgroups were defined: earning less or equal to 1 minimum wage and more the one minimum wage.

During the structured interview (Stage 1, Figure 3) patients were asked if they were affected by other comorbidities. Comorbidities scored were: hypertension (HYP), dyslipidaemia (DYS), osteoarticular disease (OA), cardiac and vascular disease (CVD), depressive disorder previous diagnostic (DEP), gastrointestinal disease (GID), genitourinary disease (GUD), diabetes mellitus (DM), respiratory disease (RESP), haematology disease (HEMATO), oncology disease (ONCO), neurodegenerative diseases (NEURO) and excessive alcohol use (ALCOHOL). The answers were validated in Stage 2 (Figure 3) by consulting the clinical records; only the comorbidities identified in the clinical records were accepted, this is further described below. For purposes of data analyses by SPSS the presence of a given comorbidity in a given individual was organized as a Yes/No answer in the SPSS.

The clinical interview also comprised cognitive evaluation tests (Figure 3). Cognitive evaluations and dementia screening tests, irrespective of the clinical diagnosis, were performed during the clinical interview. These included CDR [100], Mini Mental State Examination (MMSE) [178], Geriatric Depression Scale (GDS) [139],

Katz Index to study of Activities of Daily Living (ADL) [128] and Instrumental Activities of Daily Living (IADL) [130,179]. The tests CDR, MMSE, GDS and IADL had all been previously standardized for the Portuguese population [98,108]. The methodology used for each of these tests is well established and was presented in the introduction and their application in the pcb-Cohort is described below in the order in which they were applied to the participants during the clinical interview.

3.4 Validating Comorbidities

Access to clinical data compiled by physicians and health professionals, was made possible via collaboration with the medical staff at all the sites. Clinical data was pooled, and comorbidities confirmed and scored, other relevant information was also registered. These results are based on the international disease code that is recorded in the patient's computerized clinical files.

Pathologies indicated by the participants were further validated, by cross-referencing with the medical files. For individuals scoring positive for arterial HYP this was also validated, by confirming that they fulfilled the General Direction of Health (Direcção Geral de Saúde-DGS) guidelines for HYP ("Arterial Hypertension: definition and classification", Nº 020/2011 of 09/28/2011 with update on 3/19/2013) [10]. A HYP diagnosis is defined as the persistent elevation of systolic blood pressure (SBP) equal to or greater than 140 mmHg and / or diastolic blood pressure (DBP) equal to or greater than 90 mmHg in several temporally distinct measurements, with a level of evidence “A”, degree of recommendation “I” [180].

The second comorbidity re-evaluated according to the DGS standards was DYS. The latter involves evaluating for total cholesterol, HDL cholesterol, and triglycerides, following a 12-hour fasting period and subsequently at a minimum interval of 4 weeks the laboratory analyses should be repeated. Only then should therapy be initiated. It is important to rule out secondary and frequent causes of DYS. Patients scoring positive for osteoarticular disease (OA) had to meet clinical and/or imaging criteria for orthopaedic, rheumatologic and bone diseases. Regarding depression, the study was not designed for detailed application of all the DSM-5 criteria. Effectively the clinical

history of the participants and whether they were using antidepressants, of any class, for purposes other than symptoms of depression was checked.

Regarding diseases of the cardiovascular system, in the work here presented, these were all grouped (cardio pathologies, cardio arrhythmias, myocardial infarction, acute coronary syndrome, coronary revascularization or other arterial revascularization procedure, ischemic stroke, peripheral arterial disease). Cardiovascular risk was not investigated and therefore these individuals are not specifically addressed in the study.

Another relevant comorbidity to the study here described is diabetes. Standard references for diabetes diagnosis rely on the following parameters for plasma in the general population [181]:

a) Fasting glycaemia ≥ 126 mg / dl (or ≥ 7.0 mmol/l); or

b) Classic symptoms + occasional glycaemia ≥ 200 mg / dl (or≥11.1 mmol/l); or

c) Glucose ≥ 200 mg / dl (or ≥ 11.1 mmol/l) at 2 hours in the glucose tolerance test with 75g of glucose; or

d) Glycated haemoglobin A1c (HbA1c) ≥ 6.5%.

Thus, for individuals in the pcb-Cohort, involved in this study they were only scored positive for diabetes if one or more of the above parameters was fulfilled. Additionally, individuals with glucose intolerance were also scored positive for this work.

Gastrointestinal diseases (GID) were enumerated according to endoscopy and colonoscopy results, which were available for the volunteers; in addition to the analysis of the complaints in the consultations by the attending physicians. Special attention was given to dyspepsia. This pathology obeys the criteria of ROMA II and ROMA III [182,183] . Briefly, dyspepsia is described as chronic or recurrent pain, burning or discomfort with unpleasant subjective sensation, which may be associated with early satiety, postprandial embankment, nausea, vomiting, bloating, abdominal distension, located in the upper abdomen, with the absence of probable organic disease justifying the symptoms and absence of evidence that the symptoms improve or are associated with changes in the rate or characteristics of intestinal bowel movements. In addition, the symptoms have a minimum duration of 3 months (12

weeks), continuous or intermittent, and present at least for 6 to 12 previous months of history according to the ROMA II and III consensuses [182,183]. Therefore, in the group of diseases of the gastrointestinal tract are grouped dyspepsia, esophagitis, gastritis, duodenitis, inflammatory bowel diseases, diverticulosis, diverticulitis and anusitis.

The clinical files of the patients were thoroughly investigated. All other comorbidities were scored positive based on a previous diagnosis with confirmation by a specialist in the reference hospital for the Aveiro Region. Comorbidities not confirmed were not included when scoring for the prevalence of the different diseases.

3.5 Applying the CDR and MMSE tests

Following the structured interview, the cognitive evaluation was performed (Figure 3) initiating with the CDR test. For this test a series of questions were asked to the participant taking six parameters into account, as described in the introduction (memory, orientation, capacity to resolve problems, activities in the community, activities at home and personal care). An example of the exact questionnaire used can be found in annex III. The questionnaire has been well validated and standard scoring procedures were applied. To summarize, a 0 to 3 score was applied [98,100] also explained in detail in the introduction, where 0=Normal, 0.5=suspect, questionable or very mild dementia, and CDR≥1 (1, 2, 3) that is mild, moderate and severe dementia. The individual patient scores were submitted for SPSS for analyses. The results obtained are shown in the results chapter. The MMSE was also applied and scored from 0-30 [107]. Cut-offs were set, based on normalization for the Portuguese population [108]: 0-2 years of literacy cut-off 22; 3-6 years of literacy cut-off 24; ≥7 years of literacy cut-off 27. Those equal to or below the cut-off were scored as having cognitive deficit, those above the cut-off as normal. The procedures are well validated, as described in the introduction.

3.6 Applying the GDS

Following the structured interview, the patients underwent another screening test (Stage 1, Figure 3): the 15 item Geriatric Depression Scale (GDS15) [157]. Standard procedures, described in the introduction (Table 4), were employed. For the actual questionnaire implemented please refer to annex III.

Briefly: GDSQn corresponds to the number of the question in the original GDS15 questionnaire. The questions in the original scale are explained in table 4 (Introduction): GDSQ1 (Q1=question 1)- Are you basically satisfied with your life?; GDSQ2- Have you dropped many of your activities and interests?; GDSQ3- Do you feel that your life is empty?; GDSQ4- Do you often get bored?; GDSQ5- Are you in good spirits most of the time?; GDSQ6- Are you afraid that something bad is going to happen to you?; GDSQ7- Do you feel happy most of the time?; GDSQ8- Do you often feel helpless?; GDSQ9- Do you prefer to stay at home rather than going out and doing new things?; GDSQ10- Do you feel you have more problems with memory than most?; GDSQ11- Do you think it is wonderful to be alive now?; GDSQ12- Do you feel pretty worthless the way you are now?; GDSQ13- Do you feel full of energy?; GDSQ14- Do you feel that your situation is hopeless?; GDSQ15- Do you think that most people are better off than you are?

The score of this scale ranges from 0 to 15. The quotation GDS15 is: 1 point for the answers "Yes" in the questions 2,3,4,6,8,9,10,12,14,15; 1 point for the answers "No" in the questions: 1,5,7,11,13. The final score indicates the number of depressive symptoms. Scores 0-4 are considered normal; 5-8 indicate Mild Depression; 9-11 indicate Moderate Depression; and 12-15 indicate Severe Depression [184,185].

For experimental purposes other analyses of the GDS were performed. Among these was the shorter version considering 4 items (4 questions – question 1, question 3, question 6 and question 7, from the GDS15 question list above). This shorter version was previously proposed in the literature (GDS4Lit) as a short tool to screen for depression [186] . The score in the GDS4Lit is from 0-4, where the cut off is 1. That is scores 2-4 are indicative of a depressive state, whereas 0 and 1 are indicative of a non-

depressive status. In the study here presented other GDS shorter versions, considering fewer questions, were likewise explored, as explained in the results section.

3.7 Applying the ADL and IADL tests

Also during the clinical interview participants in the pcb-Cohort were scored with respect to ADL using the Katz score [128] and IADL [129]. For the ADL, questions were asked following a standard questionnaire (see annex III) and scoring was as follows: A to G, where A is independent, with an increasing dependence, to G which is dependent for all activities. For analytical purposes individuals were divided into two groups; independent (those scoring A) and denoted a 0 in the SPSS or dependent (all others B-G) and denoted a 1 in the SPSS.

For the IADL, questions were asked following a standard questionnaire (see annex III). Scoring observed a validated scale of 8-30, where 8 reflects independent individuals for all activities, 9-20 means moderate dependence and more than 20 means severe dependence. For analytical purposes individuals were divided into two groups; independent (those scoring 8) and denoted a 0 in the SPSS or dependent (all others) and denoted a 1 in the SPSS.

3.8 Applying the DSM-5

Subsequently, to add further clinical relevance to the data collected the DSM-5 was applied to identify profiles consistent with cognitive deficits. For cognitive impairment the criteria applied were as identified in table 1 (Introduction). The quantitative test applied for fulfilling one of the stipulated criteria DSM-5 was the CDR. In summary, individuals in the pcb-Cohort were profiled as exhibiting no deficit, mild or major neurocognitive disorder in line with DSM-5 (entered as 0,1 or 2 respectively in the SPSS). These values were used for comparative purposes and are presented in the results chapter.

For DSM-5 to evaluate depressive disorders, the criteria applied should be as identified in table 3 (Introduction). These criteria consider the number of seizures, at least two, and duration of symptoms, which must be at least 2 weeks and usually,

tends to be recurrent. Unfortunately, the original survey did not provide all the questions that were sufficient to apply the criteria for depressive disorders based on the DSM-5. Therefore, in the pcb-Cohort, a diagnosis of depression was accepted only when given by the family doctor with the support of the external consultation of psychiatry in the reference hospital of the region.

3.9 Blood Collection and Genotyping

Of the 590 participants, 508 provided a blood sample upon arrival and prior to the interview (Figure 4). For each volunteer, blood was collected into 3 EDTA-tubes (whole blood, and for serum and plasma processing; 3+5+5ml respectively), according to standard procedures. Samples were immediately aliquoted and frozen at-80°C.

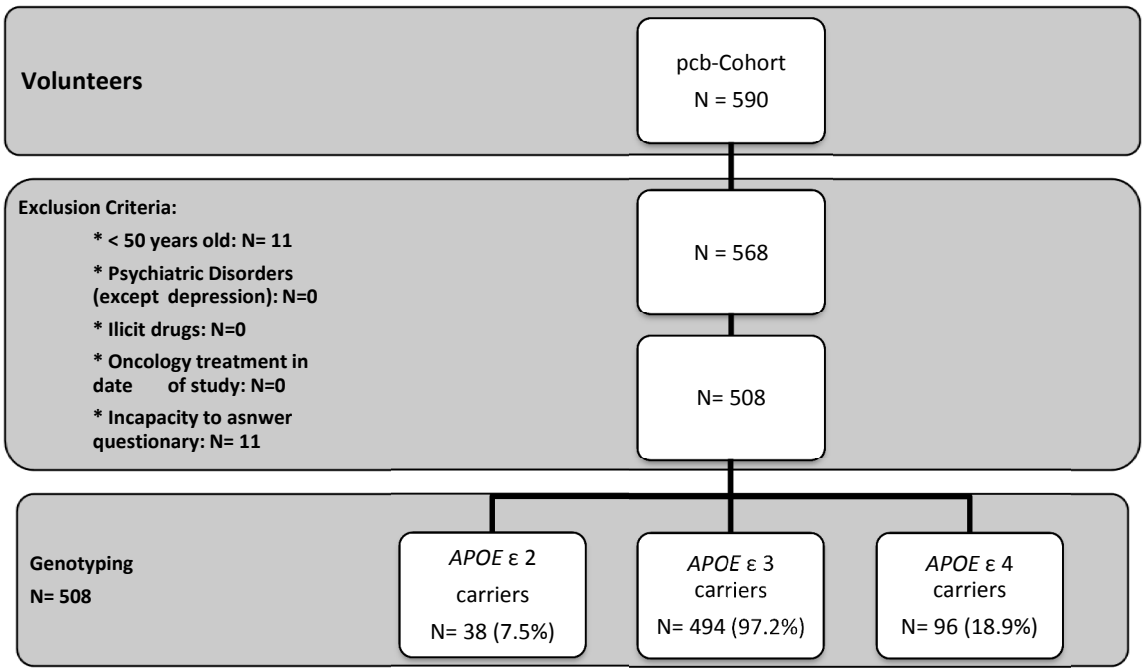


Figure 4 Study design for *APOE* genotyping
A total of 590 volunteers participated. Having applied the inclusion and exclusion criteria, 568 patients remained. From these only 508 provided blood samples. *APOE*: Genotyping for Apolipoprotein E allele'sε2,ε3 andε4 was carried out.

APOE genotyping (Figure 4) was carried out by blood direct PCR using a modified Phusion Hot Start II High-Fidelity DNA Polymerase (Phusion Blood Direct PCR Master Mix, Thermo Scientific). Briefly, PCR of the *APOE* polymorphic regions was performed using 1-2µL of whole blood from each patient, 2x Phusion Blood Direct Master Mix

(Thermo Scientific), 1M betaine (Sigma-Aldrich) and 0,5µM of each primer (APOE-Fw 5'-CGGGCACGGCTGTCCAAGGAG-3' and APOE-Rev 5´-CACGCGGCCCTGTTCCACCAG-3´). PCR conditions were: 98°C for 5min; 35 cycles of 98°C for 1s, 64°C for 5s and 72°C for 15s; and a final extension step at 72°C for 1min. This reaction yields a 303 bp PCR product. Following purification with sodium acetate (3M, pH5.2) the resulting products were sequenced with the APOE-FW primer. Results were analysed to determine the nucleotide polymorphisms and the respective *APOE* genotype.

For the study design, the number of volunteers, and the *APOE* frequencies in the pcb-Cohort were 590 and 508, respectively and this numbers were representative to population of the Aveiro district (the total population is 78450 habitants) [187,188].

3.10 Medication Usage

3.10.1 Study Design

The study design for medication usage in the pcb-Cohort is depicted in Figure 4. The pcb-Cohort has been extensively characterized and this data has been published [189]. Of the 590 volunteers, 366 participants fulfil the Beers Criteria (are 65 years old or more) and official records were available for 361 of those patients.

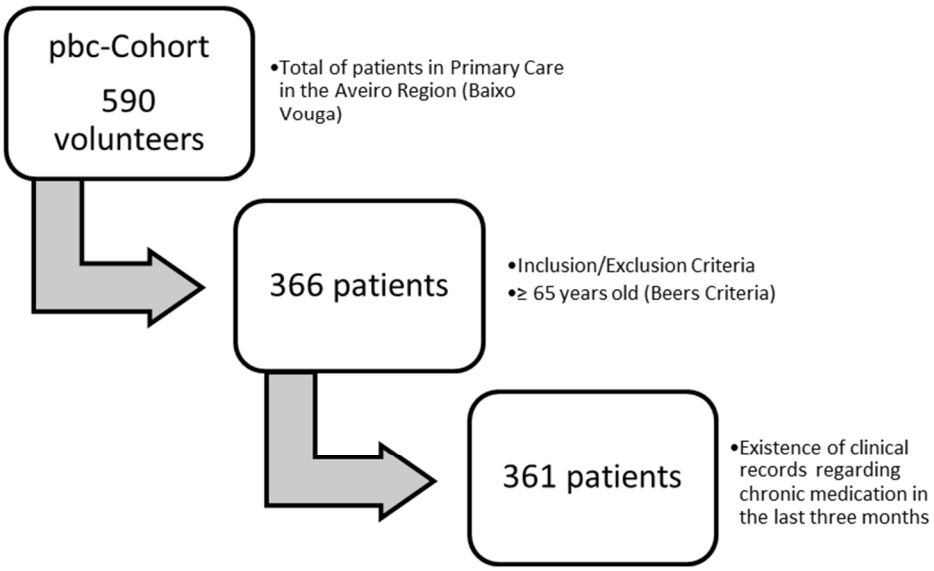


Figure 5 Study design for medication usage in the pcb-Cohort
A total of 590 volunteers from the Aveiro Region (Baixo Vouga), Portugal, participated. Beers Criteria were applied to individuals above 65 years old. In this cohort, there are 366 patients ≥ 65 years old fulfilling the criteria. Details on medication usage were available for 361 of these participants. Official records were considered for the last 3 months of medication use, prior to data collection.

The medications used by the pcb-Cohort patients were searched in the medical record of each patient. Drugs used over the last three months prior to the data collection were considered. For all subjects, a careful review of the computerized medical histories and the prescription records was performed. The Regional Health Care System made the official information available. Information regarding chronic medication use was possible for 361 patients.

3.10.2 Instruments

Standard questionnaires, were as already described and as reported in Rosa IM et al [189], regarding sociodemographic characteristics, clinical information and cognitive tests the above mentioned instruments were used to collect the data. Beers Criteria were applied to search for PIM (Potentially Inappropriate Medication) within the pcb-Cohort.

3.11 Statistical Analyses

In all stages of the statistical analyses, the database was organized and analysed using SPSS version 25. P-value<5% was considered to determine significance. Categorical variables were assessed through examination of frequencies, while continuous variables were assessed through generation of descriptive (means, standard deviations) methods to investigate the differences in the group (CDR, cognitive performance, depression groups, *APOE* carriers, polypharmacy, PIM use vs. normal groups).

3.11.1 Bivariate Analysis

Group comparisons for demographic, clinical, and global cognitive variables were performed with analyses of variance (ANOVAs) and independent samples *t* tests or Chi square ($\chi 2$) tests, as appropriate. The correlations' analyses were carried and adjusted based on the Bonferroni methods. This method was used to initially compare all the mainly variables.

3.11.2 Multivariate Analysis

After bivariate analysis of the data, the multivariate analysis was performed. For the dichotomous dependent variables (such as GDS and medication analysis), logistic regression was used. For dependent variables with more than three characteristics, multinomial regression was employed (such as CDR study and neurocognitive disorder study). In the statistical processing of the data through multivariate analysis by multinomial regression or logistic regression, the Odds ratio (OR) is generated. This ratio, when greater than 1, indicates a risk factor. If this ratio is less than 1 and greater than zero, it indicates protective factor. In our study, this methodology was used to identify the risk factors/protective factors involved with neurocognitive disorder.

OR was calculated for the parameters evaluated. Both AIC- Akaike's information criterion and BIC- Schwarz's Bayseian criterion, were calculated based on the log likelihood ratio (-2 Log L) to reflect the model's mediocrity. The final model proved to

be preferable to the null model [177]. A two-sided statistical test was carried out, and differences were significant if $p<0.05$.

3.11.2.1 Multivariate analysis in CDR and DSM-5 evaluation

The multivariate methods used for data processing was Multinomial Regression Analyses (MRA). MRA was performed using selected main characteristics as predictor variables for dementia (CDR=0.5 and CDR≥1) versus control status (CDR=0). This methodology was also used in data processing when the DSM-5 criteria were applied to classify neurocognitive disorders.

3.11.2.2 Multivariate analysis in GDS evaluation

For the GDS evaluation, the multivariate methods used was Logistic Regression, by the Enter method, as described in Maroco, 2011 [177] for the characterization of depression status in pcb-Cohort. To evaluate the significance of the sociodemographic, clinical and genotypic variables here studied, the quality of the fitted model employed the Hosmer-Lemeshow Goodness of fit statistic *(p*>0.05) was used. The contribution of variables for the construction of the model were examined by 2-log-likelihood *(p*<0.05). The OR with 95% confidence intervals (CI95%) was computed.

In case of the depression study, the frequency of depression suggestive responses for each specific item on the GDS15 scale was calculated. The questions in which at least 50% of respondents presented positive responses, consistent with depression, were registered.

3.11.2.3 ROC curve, sensibility, specificity, predictive positive value, predictive, negative value

In statistical analysis, Receiver Operating Characteristic (ROC) analysis is a powerful tool for measuring and specifying problems in medical diagnostic performance [177]. This analysis by means of a simple and robust graphic method, allows studying the variation of the sensitivity and specificity, for different points of

cut. The area below the ROC curve is associated with the discriminant power of a diagnostic test.

- Sensitivity (S) is the probability of a test positive in the presence of the disease, that is, assesses the ability of the test to detect disease when it is present.
- Specificity (E) is likely to give a negative test in the absence of the disease, so it evaluates the ability of the test to ward off the disease when it is absent.

Other statistical parameters that are can be calculated from the sensitivity and specificity of a test are: Positive predictive value (PPV) and Negative predictive value (NPV).

- PPV is the ratio of true positives among all positive test subjects. PPV expresses the likelihood that a patient with the positive test will have the disease.
- Negative predictive value (NPV): is the proportion of true negative among all individuals with negative test. NPV expresses the likelihood that a patient with the negative test will not have the disease.

If a test is more sensitive, the greater its negative predictive value (greater safety of the doctor that the person with the negative does not have the disease). If a test is more specific, the greater its positive predictive value (greater safety of the doctor that the person with the positive has the disease).

The ROC curve compares the true positives to false positives. This curve indicates the sensitivity on the y-axis as a function of a false positive (1-specificity) on the x-axis. The area under the curve (AUC) is a useful statistical summary for determining the accuracy of the proposed scales. A maximum score is 1; this indicates 100% true positive and 0% a false negative. The discriminating power of a diagnostic test is associated to the area under the curve (AUC) and the larger the area, the better the diagnosis test. The classification of the accuracy of the AUC: 0.9-1=excellent; 0.8-0.9=good; 0.7-0.8=fair; 0.6-0.7=poor; 0.5-0.6=fail [177]. Along with the ROC curve, all the coordinate points of the curve are also obtained. These points are useful for evaluating the best cut-off point for determining the positive and negative test results.

The choice of cut-off point will be decided by the need to increase sensitivity or specificity. It should be noted that the values of the table obtained with respect to the coordinates of the curve represent the best orientations for which we should consider the points of cuts of the short scales.

In this thesis, the ROC curve analysis was used to evaluate the accuracy based in sensibility, specificity, Positive predictive value and Negative predictive value (Figure 8, Figure 11 and Table 30).

3.11.2.4 Multivariate analyses in medication evaluation

For the medications usage study, a descriptive analysis of the results was performed by comparing the above-mentioned parameters with Tables 1-3 of the Beers Criteria (Annex I, supplementary Tables 1-3). Chi-Square was used to compare between qualitative characteristics and Student's t-test and ANOVA were used to study the average results. Pearson correlation was applied to compare the number of medications used and PIM. The risk of PIM and polypharmacy were calculated using the odd ratios from the logistic regression.

CHAPTER 4

Results

Results
4.1 Cognitive Evaluation of the pcb-Cohort

4.1 Cognitive Evaluation of the pcb-Cohort

The socio-demographic, clinical and genotypic characteristics as a function of the cognitive test scores were evaluated using the procedures described in the methods section. The DSM-5 criteria were subsequently applied to further analyse the results obtained. All the methods applied are detailed in chapter 3, examples of the questionnaires can be found in Annex III and the results are presented below.

4.1.1 Cognitive Evaluation

The pcb-Cohort includes 590 volunteers; this reduces to 568 participants upon applying the exclusion criteria, as indicated in the methods chapter. Subjects, 50 years old or more, were grouped (Table 7) with respect to CDR scores: CDR=0, 53% (N=301); CDR=0.5, 35% (N=199); and CDR≥1, 12% (N=68). The correlations between CDR test scores, and the other tests carried out, MMSE, depression (GDS) and the evaluation of activities of daily living (AIDL and ADL) are shown in table 7.

Results for the MMSE, AIDL and ADL are all expressed as a function of the grouped CDR scores (Table 7); all show a significant positive correlation. Overall, the CDR test identifies more putative dementia cases than the MMSE test (68 versus 54 positive cases, respectively). In the pcb-Cohort it appears that AIDL is more sensitive than the ADL (176 versus 31 dependent individuals respectively). GDS+ patients exhibit increasingly higher CDR scores compared to GDS- cases (GDS+ and CDR=0, 51/301 (16.9%); CDR=0.5, 87/199 (43.7%); and CDR≥1, 36/68 (52.9%) compared to GDS- and CDR=0, 250/301 (83%); CDR=0.5, 112/199 (56.3%); and CDR≥1, 32/68 (47%). AIDL and ADL percentages of independence, decrease with increasing CDR. To summarize, higher CDR scores correlate significantly with positive MMSE and GDS scores, and increasing dependence as determined by AIDL and ADL.

Table 7 Cognitive evaluation of the pcb-Cohort based on the CDR

Cognitive Tests		CDR=0 N=301	CDR=0.5 N=199	CDR≥1 N=68	Cramer's V	p-value*
MMSE	MMSE- N=514 (90.5%)	[a] 295 (51.9%)	[a] 187 (32.9%)	[b] 32 (5.6%)	0.550	**<0.001**
	MMSE+ N=54 (9.5%)	[a] 6 (1.1%)	[a] 12 (2.1%)	[b] 36 (6.3%)		
GDS	GDS- N=394 (69.4%)	[a] 250 (44.0%)	[b] 112 (19.7%)	[b] 32 (5.7%)	0.321	**<0.001**
	GDS+ N=174 (30.6%)	[a] 51 (9.0%)	[b] 87 (15.3%)	[b] 36 (6.3%)		
AIDL	Independent N=392 (69.0%)	[a] 242 (42.6%)	[b] 127 (22.4%)	[c] 23 (4.0%)	0.325	**<0.001**
	Dependent N=176 (31.0%)	[a] 59 (10.4%)	[b] 72 (12.7%)	[c] 45 (7.9%)		
ADL	Independent N=537 (94.5%)	[a] 299 (52.6%)	[b] 191 (33.6%)	[c] 47 (8.3%)	0.418	**<0.001**
	Dependent N=31 (5.5%)	[a] 2 (0.4%)	[b] 8 (1.4%)	[c] 21 (3.7%)		

Abbreviations: CDR-Clinical Dementia Rate; MMSE-Mini Mental State Examination; GDS-Geriatric Depression Scale; IADL-Instrumental Activities Daily Life; ADL-Katz Indices to Basic Activities Life. For scores and cut-offs, see methods. * Statistical Test: χ2-Chi square test; Statistical Test Association: Cramer´s V; The superscripts letters: [a,b,c] the same subscript letter denotes a subset of CDR categories whose column proportions do not differ significantly from each or at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value<0.05. % is expressed as a function of the total sample size (568 volunteers).

4.1.1.1 Sociodemographic characteristics

The pcb-Cohort was profiled with respect to sociodemographic characteristics. In the pcb-Cohort 71.3% of the participants are female, the relative gender proportion, does not change significantly with the different CDR score (68.4%, 77.4% and 66.2%, for scores of 0, 0.5 and ≥1 respectively), (Table 8).

For different parameters, significant differences are evident when the cohort is grouped by age. In the age group 50 to 64 years, 64 individuals (32.2%) score CDR=0.5. This is a significant at risk group that should be monitored. Likewise, a younger but smaller group, the 10.3% (7 individuals) with a CDR≥1 and less than 65 years old, represent potential early onset cases of dementia and should also be closely monitored. Consistently, mean age increases significantly with increasing CDR score from 65.8±8.9, to 67.7±8.5 to 75.4±8.5 (Table 8).

For the pcb-Cohort 'Living Arrangement', is not significant with respect to performance based on the CDR. Marital and Professional Status, have moderate significance and Monthly Family Income is statistically significant (=0.057) Of note

19.1% (13 individuals) scoring CDR≥1 are part of the active population (Professional Status). However, the data should not be over interpreted in cases where the sample number is small.

Table 8 CDR scores as a function of sociodemographic characteristics in the pcb-Cohort

Sociodemographic Characteristic	pcb-Cohort N=568	CDR=0 N=301	CDR=0.5 N=199	CDR≥1 N=68	p-value
Gender					
Male	163(28.7%)	95[a] (31.6%)	45[a] (22.6%)	23[a] (33.8%)	0.058*
Female	405(71.3%)	206[a] (68.4%)	154[a] (77.4%)	45[a] (66.2%)	
Age Group					
[50-64] years	202(35.6%)	131[a] (43.5%)	64[b] (32.2%)	7[c] (10.3%)	**<0.001***
[65-74] years	229(40.3%)	113[a] (37.5%)	94[a] (47.2%)	22[a] (32.4%)	
≥75 years	137(24.1%)	57[a] (18.9%)	41[a] (20.6%)	39[a] (57.4%)	
Age ≥ 65 years	366(64.4%)	17[a] (56.5%)	135[b](67.8%)	61c (89.7%)	**<0.001***
Age (years) (Mean ± SD)	67.6 ± 9.2	65.8 ± 8.9[a]	67.7 ± 8.5a	75.4 ± 8.5[b]	**<0.001†**
Marital Status					
Living with the partner	400(70.4%)	221[a] (73.4%)	139[b](69.8%)	40[a](58.8%)	0.057*
Others Situation	168(29.6%)	80[a] (26.6%)	60[b] (30.2%)	28[a](41.2%)	
Living Arrangement					
Alone	96 (16.9%)	46[a] (15.3%)	39[a](19.6%)	11[a] (16.2%)	0.445*
Accompanied	472(83.1%)	255[a] (84.7%)	160a (80.4%)	57[a] (83.8%)	
Professional Status					
Active	176(31.0%)	100[a] (33.2%)	63[a](31.7%)	13[a] (19.1%)	0.059*
Reformed	361(63.6%)	184[a] (61.1%)	123[a](61.8%)	54[b] (79.4%)	
Unemployed	31 (5.4%)	17[a] (5.6%)	13[a](6.5%)	1[a] (1.5%)	
Monthly Family Income					
≤ 1 minimum wage	176(31.0%)	76[a] (25.2 %)	68[a,b] (34.2%)	32[b] (47.1%)	**<0.001***
>1 minimum wage	392(69.0%)	225[a] (74.8%)	131[a,b] (65.8)	36[b] (52.9%)	
Education Level					
0-2 years of literacy	51 (9.0%)	8[a] (2.7%)	21[b] (10.6%)	22[c] (32.4%)	**<0.001***
3-6 years of literacy	402(70.8%)	207[a,b](68.8)	154[b] (77.4%)	41[a](60.3%)	
≥7 years of literacy	15(20.2%)	86[a] (28.6%)	24[b] (12.1)	5[b] (7.4%)	
Years of Study	5.1 ± 3.6	6.0 ± 4.0[a]	4.4 ± 2.9[b]	3.1 ± 2.6[c]	**<0.001†**

Abbreviations: SD-Standard Deviation; CDR-Clinical Dementia Rate; $*\chi^2$-Chi square test; † *F*-Anova; The superscript letters: [a,b,c] the same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. NOTE: % is expressed as a function of the total in each CDR groups (CDR Normal N=301, CDR 0.5 N=199, CDR ≥ 1 N=68). In bold, the p-value<0.05.

Additionally, there is a significant correlation between education level and CDR scores (Table 8). The baseline average (Years of Study) is 5.1 years of education. In the non-demented, CDR=0, subjects with more than 7 years formal education represent around 28.6% of the total, this value falls significantly to 12.1% and 7.4% for CDR=0.5 and CDR≥1 respectively.

4.1.1.2 Comorbidities grouped with respect to CDR evaluation

With ageing individuals are often affected by much other pathology. Participants were scored for comorbidities; pathologies affecting each of the participants were scored with respect to the conditions specifically identified in the individual's clinical records. Relevant comorbidities, that is, those that most affect the greatest number of individuals in the pcb-Cohort, are hypertension (HYP), dyslipidaemia (DYS), osteoarticular disease (OA) and cardiac and vascular diseases (CDV); 61.8%, 58.6%, 53.7% and 53.2%, respectively (Table 9). Other comorbidities affecting a significant percentage of the pcb-Cohort are depression (DEP) 32%, gastrointestinal disease (GID) 26.6%, genitourinary disease (GUD) 21.5% and diabetes (DM) 20.2%. Prevalence is lower for individuals with respiratory (RESP) 16.4%, haematological (HEMATO) 10.6%, oncological (ONCO) 5.6%, neurophatologies (NEURO) 3.9% diseases and excessive alcohol use 2.5%.

Table 9 Correlation between gender and comorbidities in the pcb-Cohort

Comorbidities	pcb-Cohort N=568	Gender		p-value*
		Male N=163	Female N=405	
HYP	351 (61.8%)	101[a] (62.0%)	250[a] (61.7%)	0.958
DYS	333 (58.6%)	92[a] (56.4%)	241[a] (59.5%)	0.502
OA	305 (53.7%)	53[a] (32.5%)	252[b] (62.2%)	**<0.001**
CVD	302 (53.2%)	95[a] (58.3%)	207[a] (51.1%)	0.121
DEP	182 (32.0%)	22[a] (13.5%)	160[b] (39.5%)	**<0.001**
GID	151 (26.6%)	31[a] (19%)	120[b] (29.6%)	**0.010**
GUD	122 (21.5%)	49[a] (30.1%)	73[b] (18.0%)	**0.002**
DM	115 (20.2%)	36[a] (22.1%)	79[a] (19.5%)	0.489
RESP	93 (16.4%)	20[a] (12.3%)	73[a] (18.0%)	0.094
HEMATO	60 (10.6%)	9[a] (5.5%)	51[b] (12.6%)	**0.013**
ONCO	32 (5.6%)	6[a] (3.7%)	26[a] (6.4%)	0.200
NEURO	22 (3.9%)	6[a] (3.7%)	16[a] (4.0%)	0.880
ALCOHOL	14 (2.5%)	12[a] (7.4%)	2[b] (0.5%)	**<0.001**

Abbreviations: CDR-Clinical Dementia Rate; HYP-Hypertension arterial; DYS-Dyslipidaemia; OA-Osteoarthicular disease; CVD-Cardiac and vascular Disease; DEP-Depression; GID-Gastrointestinal Disease; GUD-Genitourinary Disease; DM-Diabetes Mellitus; RESP-Respiratory Disease; HEMATO-Hematologic Disease; ONCO-Oncology Disease; NEURO-Neuropathologies; ALCOHOL-Alcohol Excessive Use. ∗ Statistical test: χ^2-Chi square test. The superscript letters: [a,b,c] the same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value<0.05. % is expressed as a function of the total for each of the columns (N=568, N=163 and N=405 respectively).

Close analysis of the prevalence of distinct comorbidities with respect to gender revealed some significant correlations. OA and DEP significantly affect more women than men with a p-value<0.001. In contrast men have a significantly higher prevalence of GUD and alcohol use, p-value=0.002 and<0.001, respectively. Two more comorbidities significantly affect women more than men, namely HEMATO and GID, at a p-value of 0.013 and 0.010, respectively. In general terms these results are in line with the distinct conditions that affect the different genders and further discussed in the discussion chapter.

Subsequently, comorbidity prevalence was evaluated with respect to the CDR scores (Table 10). A significant correlation (p<0.001) is obvious with NEURO, where the % of individuals affected rises from 0.7% (CDR=0), to 4% (CDR=0.5) to 17.6% (CDR≥1). Significant differences are also evident for OA and GID, but only for CDR=0.5 and not for CDR≥1. A possible explanation is that the N is smaller for CDR≥1 (Table 10). Depression is moderately significant (p=0.052) with respect to cognitive performance and RESP is significant p<0.047. In patients with OA (Table 10), there is a higher proportion of suspected cognitive impairment (CDR=0.5), with statistical significance (p=0.008). The same is observed for patients with GID, there is a higher proportion of patients with suspected cognitive performance (CDR=0.5), with statistical significance. It should also be noted that patients with respiratory pathologies present a significant tendency for mild cognitive impairment (CDR=0.5). Undoubtedly, patients with neurodegenerative disease have a more pronounced cognitive deficit (CDR≥1).

Table 10 Comorbidities and Clinical Dementia Rate evaluation in the pcb-Cohort

Comorbidities	pcb-Cohort N=568	CDR=0 N=301	CDR=0.5 N=199	CDR≥1 N=68	p-value*
HYP	351 (61.8%)	185[a] (61.5%)	122[a] (61.3%)	44[a] (64.7%)	0.870
DYL	333 (58.6%)	175[a] (58.1%)	119[a] (59.8%)	39[a] (57.4%)	0.910
OA	305 (53.7%)	150[a] (49.8%)	124[b] (62.3%)	31[a] (45.6%)	**0.008**
CDV	302 (53.2%)	154[a] (51.2%)	112[a] (56.3%)	36[a] (52.9%)	0.532
DEP	182 (32.0%)	83[a] (27.6%)	73[a] (36.7%)	26[a] (38.2%)	0.052
GID	151 (26.6%)	61[a] (20.3%)	73[b] (36.7%)	17[a,b] (25.0%)	**<0.001**
GUD	122 (21.5%)	63[a] (20.9%)	44[a] (22.1%)	15[a] (22.1%)	0.944
DM	115 (20.2%)	66[a] (21.9%)	36[a] (18.1%)	13[a] (19.1%)	0.562
RESP	93 (16.4%)	41[a] (13.6%)	43[b] (21.6%)	9[a] (13.2%)	**0.047**
HEMATO	60 (10.6%)	39[a] (13.0%)	16[a] (8.0%)	5[a] (7.4%)	0.142
ONCO	32 (5.6%)	18[a] (6.0%)	11[a] (5.5%)	3[a] (4.4%)	0.877
NEURO	22 (3.9%)	2[a] (0.7%)	8[b] (4.0%)	12[c] (17.6%)	**<0.001**
ALCOHOL	14 (2.5%)	10[a] (3.3%)	3[a] (1.5%)	1 (1.5%)	0.376

Abbreviations: CDR-Clinical Dementia Rate; HYP-Hypertension arterial; DYS-Dyslipidaemia; OA-Osteoarthicular disease; CVD-Cardiac and vascular Disease; DEP-Depression; GID-Gastrointestinal Disease; GUD-Genitourinary Disease; DM-Diabetes Mellitus; RESP-Respiratory Disease; HEMATO-Hematologic Disease; ONCO-Oncology Disease; NEURO-Neuropathologies; ALCOHOL-Alcohol Excessive Use. ∗ Statistical test: χ^2-Chi square test. The superscript letters: [a,b,c] the same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value<0.05. NOTE: % is expressed as a function of the total in each of the CDR groups (CDR 0 N=301, CDR 0.5 N=199, CDR ≥ 1 N=68).

Given the high correlation with GID, this was evaluated in more detail (Table 11). The individual clinical records of the 151 clinically referenced GID positive participants were consulted. Thus, it was possible to determine the specific GID pathologies affecting the patients (Table 11) but also that 4 of the patients diagnosed with Glucose Intolerance were classified as DM in this study. Clearly particular attention should be paid to the number of patients diagnosed with gastrointestinal tract disease.

Table 11 Breakdown of conditions included in gastrointestinal diseases

Types of Gastrointestinal disease	Total
No GID	417
Dyspepsia	116
Gastritis	8
Diverticulosis	5
Hepatic Steatosis	5
Esophagitis / GERD / Hernia	3
Anusite	3
Esophagitis / GERD / Hernia + Gastritis	2
Diverticulosis + Gastritis	2
Intestinal polyp	1
Cancer	1
Others	5
Intestinal Inflammatory disease	0
Total	568

Abbreviation: GID=Gastrointestinal Disease; GERD=Gastroesophageal Reflux disease

In the pcb-Cohort the GID that most affects participants are dyspepsia (116 out of 151), this is followed by gastritis (8 out of 151) but in much lower numbers (Table 11). Affecting only 5 individuals are diverticulosis and hepatic steatosis. The other conditions affected 1 to 3 individuals.

4.1.1.3 Correlation between CDR status and APOE genotyping

Apolipoprotein E (APOE) is a cholesterol carrier supporting lipid transport and the highest genetic risk factor for dementia thus far identified [190–193]. The gene has three alleles;ε2,ε3, andε4. For the pcb-Cohort blood was collected, but only possible for 508 individuals. The pcb-Cohort genotypes areε2ε3 (N=31; 6.1%),ε2ε4 (N=7;1.4%),ε3ε3 (N=381;75.0%),ε3ε4 (N=82;16.1%) andε4ε4 (N=7;1.4%). The most common allele in the pcb-Cohort isε3 (Table 12), found in more than half of the general population, and the most abundant (97.2%). The allele frequency was then considered as a function of the CDR score. Relativelyε4 carrier percentages increase significantly with increasing CDR; 15.6% at CDR=0, almost doubling to 29.7% for CDR ≥1. Thus, theε4 allele represents a significant risk factor. In contrast theε2 allele carriers are more represented in CDR=0 than in CDR≥1, consistent with its protective role.

Table 12 Correlation of CDR groups and *APOE* allele's carriers

APOE allele carriers		pcb-Cohort	CDR=0 N=256	CDR=0.5 N=188	CDR≥1 N=64	p-value*
ε2	Non ε2	470 (92.5%)	[a] 233 (91.0%)	[a] 176 (93.6%)	[a] 61 (95.3%)	0.390
	ε2	38 (7.5%)	[a] 23 (9.0%)	[a] 12 (6.4%)	[a] 3 (4.7%)	
ε3	Non ε3	14 (2.8%)	[a] 4 (1.6%)	[a] 7 (3.7%)	[a] 3 (4.7%)	0.234
	ε3	494 (97.2%)	[a] 252 (98.4%)	[a] 181 (96.3%)	[a] 61 (95.3%)	
ε4	Non ε4	412 (81.1%)	[a] 216 (84.6%)	[a, b] 151 (80.3%)	[b] 45 (70.3%)	**0.035**
	ε4	96 (18.9%)	[a] 40 (15.6%)	[a, b] 37 (19.7%)	[b] 19 (29.7%)	

Abbreviations: CDR-Clinical Dementia Rate; *APOE ε2*,ε3,ε4: Apolipoprotein E alleleε2,ε3,ε4, respectively; *APOE* genotyping was carried out for 508 voluntaries (from which the blood was available). Statistical test: *χ2-Chi square test. [a,b,c] the same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions that differ significantly from each other at the 0.05 level. In bold, the p-value<0.05. NOTE: For the pcb-Cohort column % is expressed as a function of the total sample size, 508 volunteers. Data in the other columns are represented as a function of each of the CDR group.

4.1.1.4 Multivariate Analyses based on CDR status

For an overall analysis, an all-in-one multivariate data analysis was employed Table 13 shows multivariate analysis to identify risk factors. Literacy, Age, Gender, ADL, IADL, GID, NEURO and *APOE ε2*, contribute significantly to the multinomial regression and therefore to cognitive performance (Likelihood Ratio Test-Table 14). The reference CDR=0 group was compared to CDR=0.5 and CDR≥1 groups (Table 11). Whereas some parameters/risk factors are sustained in both analyses, others are more relevant in only one of the sets. For instance, comparing CDR=0 to CDR=0.5 individuals, the *APOE ε2* carriers, have a 64% (% of 1-0.36; OR=0.36; CI 0.15-0.88; *p*=0.025) less chance of scoring CDR=0.5 compared to the non-*APOE ε2* carries. This is not so for CDR=0 against CDR≥1. In fact, being anε2 carrier is no longer significant, but rather, significance is associated withε4 carriers. *APOE ε4* carriers, compared to *APOE ε4* non-carriers, have a 2.30 greater chance of scoring CDR≥1.

Some parameters are significant in only one of the multinomial regressions (Table 13). Age is not significant in the CDR=0 vs CDR=0.5 but is for CDR≥1. For the latter, in the age group 50-64, there is an 87% (% of 1-0.13; OR=0.13; CI: 0.040-0.39; p=0.000) less chance of scoring CDR≥1, compared to the older age group. This percentage falls to 51% (% of 1-0.49; OR=0.49; CI: 0.225- 1.08; p=0.078) when the age

groups compared are 65-74 versus 75-90. In other words, higher age groups correlate significantly with higher CDR scores. ADL also varies between the two multinomial regressions. In the CDR=0 vs the CDR=0.5 there is no correlation, but in the CDR=0 vs the CDR≥1, dependent patients are 19.36 times more likely to score CDR≥1. Gender, likewise, did not produce the same results across both analyses. No significance was detected in CDR=0 vs CDR≥1, but gender is significant for CDR=0 vs CDR=0.5. In fact, females have a 1.70 greater chance of scoring CDR=0.5, compared to males. Unexpectedly this finding is not sustained in CDR≥1, this may be linked to the fact that life expectancy in Portugal is around 75 years [194]. Thus, the older age group, which is 75-90 years old, is highly impacted by life expectancy.

Other significant parameters in both multinomial regressions are Literacy, IADL, NEURO and GID. Literacy correlates with dementia [195,196]. In the CDR=0 vs the CDR=0.5, patients with low literacy (0-2 years) are around 7.40 times more likely, than those with relatively higher literacy (>7 year), to score CDR=0.5; and patients with 3-6 years of literacy are 2.50 times more likely. This correlation is even more accentuated in the CDR=0 vs the CDR≥1 multinomial regression analyses. Patients with low literacy (0-2 years) have 35.28 times more chance of scoring CDR≥1, compared to the higher literacy group (>7 years). Likewise, patients with 3-6 years of literacy have 3.95 times more chance of scoring CDR≥1 (Table 13). With increasing dementia, patients become more dependent. In the CDR=0 vs CDR=0.5, volunteers who are dependent (IADL), have a 2.24 greater chance of scoring CDR=0.5 compared to independent volunteers. This rises to 3.47 in the CDR≥1 group. A similar trend is evident with respect to NEURO. Participants with a neuropathology are at a 5.06 times greater risk of scoring CDR=0.5 and 17.52 times of scoring CDR≥1.

Completely unexpected, and to our knowledge, hitherto unreported, is the association between cognitive performance as determined by CDR scores and GID. In the CDR=0 vs CDR=0.5 or CDR≥1 regression analyses, patients with GID, have a 2.55 or 2.29 greater risk of scoring the respective higher CDR score.

Table 13 Multivariate analyses to identify risk factors

Parameters	CDR=0.5[a]		CDR≥1[a]	
	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Intercept		0.413		0.105
APOE ε2 carriers	0.36 (0.15-0.88)	**0.025**	0.25 (0.04-1.45)	0.130
APOE ε3 carriers	0.28 (0.06-1.20)	0.087	0.37 (0.03-4.03)	0.412
APOE ε4 carriers	1.20 (0.68-2.13)	0.522	2.30 (0.98-5.39)	0.055
Female	1.70 (1.01-2.84)	**0.044**	1.06 (0.46-2.42)	0.890
50-64 years	1.00 (0.55-1.82)	0.992	0.13 (0.04-0.39)	**<0.001**
65-74 years	1.16 (0.66-2.04)	0.615	0.49 (0.23-1.08)	0.078
75-90 years	---	---	---	---
0-2 years of Literacy	7.41 (2.64-20.82)	**<0.001**	35.28 (7.25-171.70)	**<0.001**
3-6 years of Literacy	2.50 (1.4-4.46)	**0.002**	3.95 (1.10-14.20)	**0.035**
≥ 7 years of Literacy	---	---	---	**---**
Dependent ADL	4.01 (0.73-22.85)	0.108	19.36 (3.22-116.60)	**0.001**
Dependent IADL	2.24 (1.37-3.67)	**0.001**	3.47 (1.62-7.45)	**0.001**
HYP	0.80 (0.51-1.26)	0.343	1.05 (0.48-2.28)	0.905
OA	1.15 (0.74-1.79)	0.529	0.70 (0.33-1.46)	0.333
DEP	1.10 (0.69-1.77)	0.679	1.92 (0.88-4.20)	0.101
GID	2.55 (1.56-4.16)	**<0.001**	2.29 (1.01- 5.20)	**0.047**
DM	0.68 (0.39-1.16)	0.155	0.83 (0.35-1.95)	0.670
NEURO	5.06 (0.99-25.62)	**0.050**	17.52 (2.8-108.70)	**0.002**

Abbreviations: OR-risk or protective values in each parameter studied (CI-confidential Interval of OR; *APOE:* Genotypingε2/ε3/ε4 alleles; ADL: Activity daily of life; IADL: Instrumental Activity daily life; HYP-Hypertension; OA-Osteoarthicular disease; DEP-depression; GID-Gastrointestinal disease; DM-Diabetes Mellitus; NEURO-Neuropathologies. The superscript letter: [the] reference category is: CDR=0 or Normal Cognitive Performance; (---) This parameter is set to zero because it is redundant. It is the reference class into the parameter studied. For the other categories it is as indicated in the previous tables, i.e. male for female. If the number 1 is not within the CI, there is statistical significance. Other abbreviations are as previously indicated. In bold, the p-value<0.05.

Table 14 Internal model of the multinomial regression of cognitive performance based on CDR scores

Effect	Model Fitting Criteria			Likelihood Ratio Tests		
	AIC of Reduced Model	BIC of Reduced Model	-2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.
Intercept	705.673	849.510	637.673[a]	0.000	0	---
APOE ε4 carriers	705.219	840.595	641.219	3.546	2	0.170
APOE ε3 carriers	704.767	840.142	640.767	3.094	2	0.213
APOE ε2 carriers	707.966	843.342	643.966	6.293	2	**0.043**
Gender	706.147	841.523	642.147	4.474	2	0.107
Age Group	716.139	843.053	656.139	18.465	4	**0.001**
Literacy	731.027	857.941	671.027	33.353	4	**<0.001**
ADL	716.895	852.270	652.895	15.222	2	**<0.001**
IADL	717.093	852.469	653.093	15.420	2	**<0.001**
HYP	702.789	838.165	638.789	1.116	2	0.572
OA	703.634	839.009	639.634	1.960	2	0.375
DEP	704.364	839.739	640.364	2.691	2	0.260
GID	716.569	851.944	652.569	14.895	2	**0.001**
DM	703.730	839.105	639.730	2.056	2	0.358
NEURO	712.906	848.281	648.906	11.233	2	**0.004**

Abbreviations: OR-risk or protective values in each parameter studied (CI-confidential Interval of OR; *APOE*-Genotypingε2/ε3/ε4 alleles; ADL-Activity daily of life; IADL-Instrumental Activity daily life; HYP-Hypertension; OA-Osteoarthicular disease; DEP-depression; GID-Gastrointestinal disease; DM-Diabetes Mellitus; NEURO-Neuropathologies.

As is clearly evident the model used for the multivariate analysis is a good fit. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0. This reduced model is equivalent to the final model given that omitting the effect does not increase the degrees of freedom. The variables that contribute significantly to the final model are those identified in bold (Table 14). The *APOE* allele carriers, Age group, Literacy, ADL, IADL, GID and NEURO contribute significantly to the cognitive performance of individuals (based on the CDR test). The chi-square test statistic is the difference in-2 log-likelihoods between the final model and a reduced model.

4.1.2 Cognitive Evaluation Based on Applying the DSM-5 Criteria

In order to give further clinical relevance to the data, the DSM-5 criteria were applied to the pcb-Cohort. Thus, the data obtained, from the participants, was subsequently evaluated as detailed in table 1 in the Introduction (Chapter 1). All the criteria listed in the above mentioned table 1 were applied as well as the exclusion of

all possible cases of depression. All the questionnaires (CDR, MMSE and GDS) employed in this study are internationally validated; further questions necessary to implement the DSM-5 for depressive disorders were not included. Thus, to reliably apply the DSM-5 criteria regarding depressive disorders; depression cases considered were; all those individuals who had a clinical depression diagnosis, as well as those who scored positive in the GDS screening test.

The pcb-Cohort includes 286 individuals with normal depression evaluation (without depressive disorder plus GDS15 negative) and 282 with depressive possible cases (74 individuals with depressive disorder, 106 patients with GDS15 positive, but without definitive diagnosis of depression, plus 102 patients with history of depression but it is not possible to confirm of the diagnosis). The figure below (Figure 6) shows the methods used to select the patients for subsequent analyses.

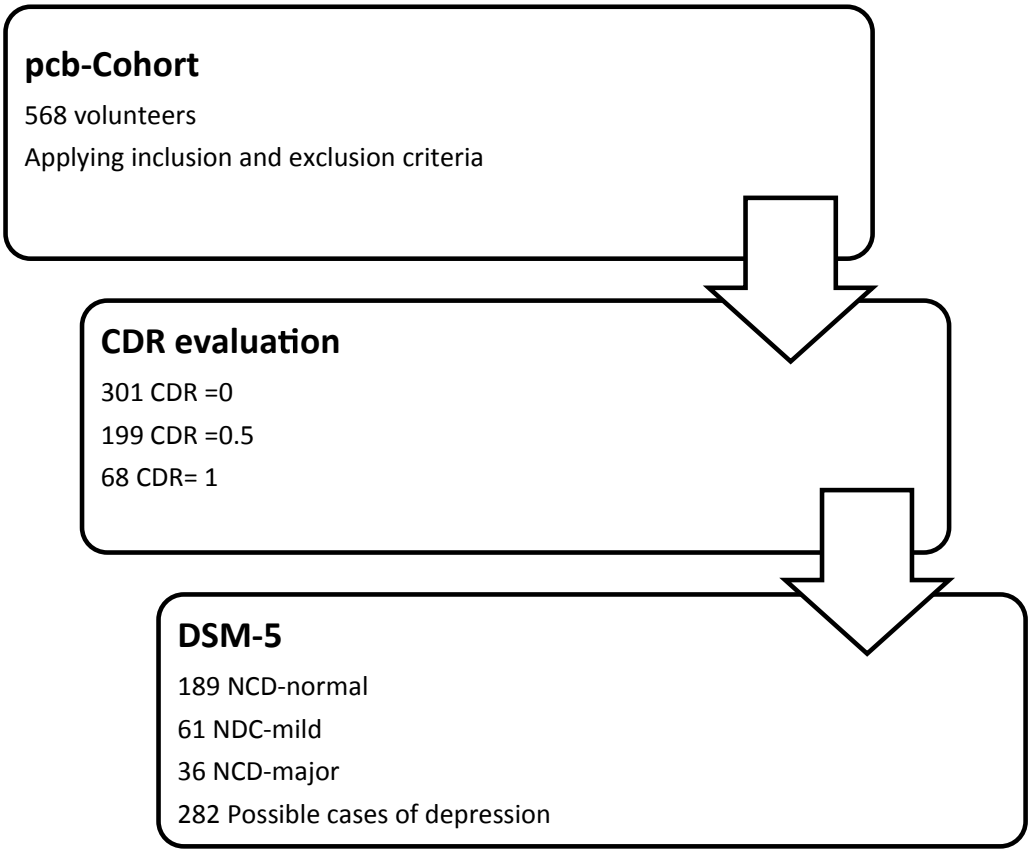


Figure 6 Selection procedure to apply the DSM-5 criteria

Abbreviations: CDR-Clinical Dementia Rate. DSM-The Diagnostic and Statistical Manual of Mental Disorders; NCD-neurocognitive disorder; NCD-normal: performance cognitive normal; NCD-mild: neurocognitive disorder mild; NCD-major: neurocognitive disorder major.

According to the DSM-5 criteria, as described in Chapter 1, cases of cognitive alteration considered cannot be explained by other mental illnesses such as major depression and schizophrenia. To obey this precept, the possible cases of depression were excluded from the neurocognitive disorder (NCD) group, but were nonetheless considered during the analyses, as explained below. The DSM-5 criteria are sub-dividing NCD into mild (NCD-mild) and major (NCD-major) cases.

Regarding depression, there are a total of 182 patients with a history of depression and a total of 174 patients with GDS positive. Of the 182 patients with depression, 108 are GDS- this may be due to medication usage and positive response to the therapeutic strategy used. Of the 174 patients with GDS-positive, for 100 subjects it was not possible to confirm that they fulfil the DSM-5 criteria for depressive disorder. Considering the 182 and 174 above mentioned putative depression cases only 74 individuals have a confirmed diagnosis and a positive GDS.

Taking all these aspects into consideration, four groups result (Figure 6); NCD-normal, NCD-mild, NCD-major and possible cases of depression (PCD).

4.1.2.1 Correlating DSM-5 based cognitive performance and sociodemographic characteristics

The pcb-Cohort was thus analysed taking into consideration the DSM-5 criteria for cognitive performance and the impact of sociodemographic characteristics addressed. The results are presented below (Table 15). The analysis shows the correlation of the individuals without cognitive impairment, those with NCD-mild, NCD-major patients, and PCD. Significant differences were evident for gender, age, living arrangement and literacy. The results (Table 15) clearly show that NCD-mild have a greater proportion: females, age group 65-74 years old, cases of patients that live alone and patients with fewer years of literacy, relative patients with NCD-normal. In cases of NCD-major, it is possible see that there is prevalence of patients who are older, (≥ 75 years old), and with fewer years of literacy (Table 15).For PCD, there are more women (82.3%) compared to men and regarding age the greatest proportion of depressed individuals is found in the age group 65-74. Other significant contributors to

depression are low monthly family income (p=0.037), living arrangement and literacy (Table 15).

Table 15 Correlation of DSM-5 based neurocognitive disorders with sociodemographic characteristics in pcb-Cohort

Characteristics	N=568 (%)	NCD-normal N=189	NCD-mild N=61	NCD-major N=36	PCD N=282	p-value
Gender						
Male	113(39.5%)	82[a] (43.4%)	13[b] (21.3%)	18[a] (50.0%)	50[b] (17.7%)	**<0.001**
Female	173 (60.5%)	107[a] (56.6%)	48[b] (78.7%)	18[a] (50.0%)	232[b] (82.3%)	
Age Group						
50-64	103 (36.0%)	80[a] (42.3%)	13[b] (21.3%)	10[a,b] (27.8%)	99[a.b] (35.1%)	**0.003**
65-74	112 (39.2%)	65[a] (34.4%)	36[b] (59.0%)	11[a] (30.6%)	117[a.b] (41.5%)	
>=75	71 (24.8%)	44[a] (23.3%)	12[a] (19.7%)	15[b] (41.7%)	66[a] (23.4%)	
Age						
<65	103 (36.0%)	80[a] (42.3%)	13[b] (21.3%)	10[a,b] (27.8%)	99[a.b] (35.1%)	**0.017**
>=65	183 (64.0%)	109[a] (57.7%)	48[b] (78.7%)	26[a,b] (72.2%)	183[a.b] (64.9%)	
Marital Status						
Living with partner	218 (76.2%)	146[a] (77.2%)	42[a] (68.9%)	30[a] (83.3%)	182[a.b] (64.5%)	**0.008**
Others Situations	68 (23.8%)	43[a] (22.8%)	19[a] (31.1%)	6[a] (16.7%)	100[b] (35.5%)	
Living Arrangement						
Alone	42 (14.7%)	25[a] (13.2%)	15[b] (24.6%)	2[c] (5.6%)	54[a] (19.1%)	**0.034**
Accompanied	244 (85.3%)	164[a] (86.8%)	46[b] (75.4%)	34[c] (94.4%)	228[a] (80.9%)	
Professional Status						
Active	84 (29.4%)	59[a] (31.2%)	19[a] (31.1%)	6[a] (16.7%)	92[a] (32.6%)	
Reformed	192 (67.1%)	122[a] (64.6%)	41[a] (67.2%)	29[a] (80.6%)	169[a] (59.9%)	0.139
Unemployed	10 (3.5%)	8[a] (4.2%)	1[a] (1.6%)	1[a] (2.8%)	21[b] (7.4%)	
Monthly Family Income						
<=1 MW	74 (25.9%)	45[a] (23.8%)	17[a] (27.9%)	12[a] (33.3%)	102[b] (36.2%)	**0.037**
>1 MW	212 (74.1%)	144[a] (76.2%)	44[a] (72.1%)	24[a] (66.7%)	180[b] (63.8%)	
Literacy						
0-2 years	18 (6.3%)	3[a] (1.6%)	7[b] (11.5%)	8[b] (22.2%)	33[b] (11.7%)	**<0.001**
3-6 years	203 (71.0%)	133[a] (70.4%)	46[a] (75.4%)	24[a] (66.7%)	199[a] (70.6%)	
>=7 years	65 (22.7%)	53[a] (28.0%)	8[a] (13.1%)	4[a] (11.1%)	50[a] (17.7%)	

Abbreviation: NCD-Neurocognitive disorder; PCD-Possible cases of depression; MW-Minimum Wage. Statistical test: *χ2-Chi square test. Values in the same row and not sharing the same superscript are significantly different at p<0.05 in the two-sided test of equality for column proportions. Tests assume equal variances. Tests are adjusted for all pairwise comparisons within a row of each innermost using the Bonferroni correction. Superscripts letters [a, b]: The same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value less than 0.05.

With respect to ageing, as expected, increasing NCD deficits are clearly evident in the older age groups (Table 15). In the younger age group, 50 to 64 years old, 42.3% exhibited NCD-normal performance and these falls to 23.3% for individuals aged 75 years old. In contrast, for the 50 to 64-year-old group, 27.8% exhibited NCD-major, whereas in the 75-year-old or more groups, this increased to 41.7% (for more details

see Table 15). The highest group however was 59% exhibiting NCD-mild in the 65-74 age groups, clearly indicating that this group should be closely followed. The proportion of cognitive impairment is higher in patients that are living with someone. In patients who are accompanied, a higher proportion of cognitive impairment is also observed. This proportion is even higher in the more NCD-major.

With respect to education, three groups were considered, 0-2 years formal education, 3-6 years formal education and more than 7 years (Table 15). The most striking, significant difference was observed in the 0-2 years literacy. In other words, 22.2% of individuals with NCD-major have 0-2 years formal education, and this percentage falls to 11.5% in NCD-mild and 1.6% in NCD-normal.

4.1.2.2 Association between cognitive performance based on DSM-5 and clinical characteristics

Comorbidity bivariate correlations with cognitive deficits, as determined by applying the DSM-5 neurocognitive criteria, were subsequently investigated (Table 16). As explained above, 286 individuals fulfil the DSM-5 criteria and the fourth group includes patients with depression or possible depression. However, for comparative purposes the prevalence of the original pcb-Cohort group (N=568) is also included in the table.

As is evident (Table 16), cognitive performance correlates with OA and RESP related disorders. This is consistent with the results when the DSM-5 criteria are not implemented (presented in 4.1.1.2). Contrary to this however GID and NEURO do not correlate with NCD when DSM-5 criteria are applied. Rather suggesting that these individuals who previously were associated with poor CDR scores are now included in the PCD group. Thus, GID in the PCD group is significantly more represented when compared to the NCD-normal (p=0.001).

Table 16 Comorbidities and cognitive performance based on DSM-5 classification for neurocognitive disorders

Comorbidities	N=568	NCD-normal N=189	NCD-mild N=61	NCD-major N=36	PCD N=282	p-value*
HYP	351 (61.8%)	115[a] (60.8%)	41[a] (67.2%)	20[a] (55.6%)	175[a] (62.1%)	0.698
DYS	333 (58.6%)	111[a] (58.7%)	38[a] (62.3%)	19[a] (52.8%)	165[a] (58.5%)	0.838
OA	305 (53.7%)	86[a] (45.5%)	30[a,b] (49.2%)	20[a,b] (55.6%)	169[b] (59.9%)	**0.018**
CVD	302 (53.2%)	101[a] (53.4%)	34[a] (55.7%)	21[a] (58.3%)	146[a] (51.8%)	0.856
GID	151 (26.2%)	34[a] (18.0%)	16[a,b] (26.2%)	6[a,b] (16.7%)	95[b] (33.7%)	**0.001**
GUD	122 (21.5%)	40[a] (21.2%)	12[a] (19.7%)	8[a] (22.2%)	62[a] (22.0%)	0.980
DM	115 (20.2%)	42[a] (22.2%)	14[a] (23.0%)	5[a] (13.9%)	54[a] (19.1%)	0.605
RESP	93 (16.4)	24[a] (12.7%)	9[a,b] (14.8%)	12[b] (33.3%)	48[a,b] (17.0%)	**0.022**
HEMATO	60 (10.6%)	24[a] (12.7%)	5[a] (8.2%)	4[a] (11.1%)	27[a] (9.6%)	0.655
ONCO	32 (5.6%)	9[a] (4.8%)	6[a] (9.8%)	0(0.0%)	17[a] (6.0%)	0.210
NEURO	22 (3.9%)	2[a] (1.1%)	4[a] (6.6%)	1[a] (2.8%)	15[a] (5.3%)	0.075
AlCOHOL	14 (2.5%)	6[a] (3.2%)	2[a] (3.3%)	1[a] (2.8%)	5[a] (1.8%)	0.767

Abbreviations: HYP-Hypertension arterial; DYS-Dyslipidaemia; OA-Osteoarthicular disease; CVD-Cardiac and vascular Disease; DEP-Depression; GID-Gastrointestinal Disease; GUD-Genitourinary Disease; DM-Diabetes Mellitus; RESP-Respiratory Disease; HEMATO-Hematologic Disease; ONCO-Oncology Disease; NEURO-Neuropathologies; ALCOHOL-Alcohol Excessive Use. Statistical test: *χ2-Chi square test. Values in the same row and not sharing the same superscript are significantly different at *p<0.05* in the two-sided test of equality for column proportions. N=568 patients of pcb-Cohort). Superscripts letters [a, b]: The same subscript letter denotes a subset of categories whose column proportions don not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value less than 0.05. Tests assume equal variances. Tests are adjusted for all pairwise comparisons within a row of each innermost using the Bonferroni correction.

4.1.2.3 Correlating DSM-5 based cognitive performance and APOE genotype

Table 17 depicts cognitive performance, based on DSM-5 criteria, with Apolipoprotein E (*APOE*) genotyping. Of the 508 individuals in the pcb-Cohort, 286 fulfil the DSM-5 criteria for NCD, of theε4 carriers 14.7% (N=24) exhibit normal cognitive performance, 24.6% (N=18) NCD-mild, 8.6% (N=3) NCD-major 21.7% (N=54) PCD. Unlike the correlation shown in table 12 there is no significant correlation between cognitive performance and *APOE* genotype. However, it must be noted that some of the groups in table 17 are too small for meaningful statistical analysis (groups with 0 or 1), this was nonetheless done for the sake of carrying out complete analyses for comparison. Therefore, care must be taken when determining conclusions.

Table 17 Correlation between cognitive performance based on DSM-5 criteria and *APOE* genotyping

***APOE* allele carriers**	**N=508**	**NCD-normal N=163**	**NCD-mild N=61**	**NCD-major N=35**	**PCD N=249**	**p-value**
ε2	Non-ε2 (N=240)	149[a] (91.4%)	59[a] (96.7%)	32[a] (91.4%)	230[a] (92.4%)	0.590
	ε2 (N=19)	14[a] (8.6%)	2[a] (3.3%)	3[a] (8.6%)	19[a] (7.6%)	
ε3	Non-ε3 (N=3)	0[1] (0.0%)	2[a] (3.3%)	1[a] (2.9%)	11[a] (4.4%)	0.064
	ε3 (N=256)	163(100.0%)	59[a] (96.7%)	34[a] (97.1%)	238[a] (95.6%)	
ε4	Non-ε4 (N=217)	139[a] (85.3%)	46[a] (75.4%)	32[a] (91.4%)	195[a] (78.3%)	0.077
	ε4 (N=42)	24[a] (14.7%)	15[a] (24.6%)	3[a] (8.6%)	54[a] (21.7%)	

Abbreviations: NCD-Neurocognitive disorder; NCD-mild- Neurocognitive disorder mild; NCD-major-Neurocognitive disorder major. NCD normal: performance cognitive normal. PCD-Possible cases of depression; *APOE*-apolipoprotein. Statistical test: *χ2-Chi square test. N=259 because there are patients that blood is not available. Values in the same row not sharing the same superscript are significantly different at p<0.05 in the two-sided test of equality for column proportions. Cells with no subscript are not included in the test. Tests assume equal variances. Tests are adjusted for all pairwise comparisons within a row of each innermost using the Bonferroni correction. More than 20% of cells in this table have expected cell counts less than 5. Chi-square results may be invalid.

4.1.2.4 Multivariate analyses of cognitive performance based on DSM-5

The reference Normal cognitive performance group was compared to NCD-mild, NCD-major and Depressive possible cases groups (Table 18). Multivariate data analysis was consequently carried out to again identify risk factor(s) in patients with NCD as identified upon applying the DSM-5 neurocognitive criteria (Table 18). Age, gender, literacy, GID and ADL correlate significantly.

Table 18 Multivariate analyses to identify risk factors based on DSM-5 classification

	NCD-mild			NCD-major			PCD		
Parameters	**Sig**	**OR**	**CI**	**Sig**	**OR**	**CI**	**Sig**	**OR**	**CI**
APOEε2 non carriers	0.100	3.877	(0.771-19.499)	0.788	1.211	(0.300-4.899)	0.241	1.629	(0.721-3.681)
APOEε4 carriers	0.053	2.133	(0.991-4.590)	0.059	0.234	(0.052-1.058)	0.068	1.700	(0.962-3.005)
Female	**0.001**	3.709	(1.761-7.813)	0.073	0.447	(0.186-1.078)	**<0.001**	3.591	(2.205-5.846)
50-64 Years old	0.524	0.735	(0.284-1.898)	0.737	0.838	(0.300-2.343)	0.910	0.966	(0.532-1.755)
65-74 years old	**0.050**	2.291	(1.001-5.244)	0.767	0.862	(0.321-2.310)	0.339	1.330	(0.741-2.388)
≥75 years old*	---			---			---		
0-2 years of education	**0.005**	10.783	(2.083-55.812)	**<0.001**	44.435	(6.646-297.099)	**0.003**	7.339	(1.934-27.856)
3-6 years of educations	0.239	1.721	(0.698-4.246)	**0.024**	4.698	(1.223-18.049)	0.127	1.533	(0.886-2.654)
≥7 years of education*	---			---			---		
HTA	0.624	1.192	(0.590-2.409)	0.360	0.676	(0.292-1.564)	0.799	0.940	(0.587-1.508)
OA	0.419	1.316	(0.676-2.563)	0.075	0.457	(0.193-1.082)	0.479	0.847	(0.536-1.340)
GID	0.389	1.396	(0.653-2.986)	0.937	0.959	(0.336-2.737)	**0.017**	1.905	(1.121-3.236)
DM	0.801	0.906	(0.422-1.948)	0.176	0.457	(0.147-1.420)	0.252	0.723	(0.416-1.259)
NEURO	0.087	4.980	(0.793-31.264)	0.333	0.247	(0.015-4.183)	0.212	2.825	(0.553-14.424)
ADL	0.843	1.345	(0.072-25.209)	**0.001**	58.117	(5.851-577.243)	**0.035**	9.562	(1.170-78.116)

Abbreviations: OR-risk or protective values in each parameters studied (CI-confidential Interval of OR); NCD-Neurocognitive disorder; NCD-mild- Neurocognitive disorder mild; NCD-major-Neurocognitive disorder major; NCD-normal-performance cognitive normal; PCD-Possible cases of depression; *APOE*- Genotypingε2/ε3/ε4 alleles; ADL-Activity daily of life; IADL- Instrumental Activity daily life; HYP-Hypertension; OA-Osteoarthicular disease; DEP-depression; GID-Gastrointestinal disease; DM-Diabetes Mellitus; NEURO-Neurodegenerative pathologies. The reference category is: NCD-normal or Normal Cognitive Performance; (---) This parameter is set to zero because it is redundant. It is the reference class into the parameter studied. For the other categories it is as indicated in the previous tables, i.e. male for female. If the number 1 is not within the CI, there is statistical significance. Other abbreviations are as previously indicated. In bold, the p-value<0.05.

APOE ε2 non-carriers do not have statistical significance as a risk factor with respect to NCD-mild or NCD-major or even PCD. *APOE ε4* carriers have 2.1 times greater chance of scoring NCD-mild and 1.7 times greater chance of scoring PCD, with moderate statistical significance (p-value=0.053 and p-value=0.068 respectively).

Gender is significant for NCD-mild. In fact, females have 3.7 times greater chance of scoring NCD-mild and 3.6 times greater chance of possible depressive cases (Table 18), compared to males (OR 3.7, CI 95% 1.7-7.8, p-value=0.001). In contrast, women are about 55% less likely to have NCD-major, compared to men (OR 0.447, CI 95% 0.186-1.078, p-value 0.073). Women have 3.6 times greater chance of scoring depressive possible cases (OR 3.6 CI 95% 2.2-5.8, p-value<0.001).

Age is likewise significant for the risk of NCD-mild, but age is not significant in NCD-Major and PCD. For the latter, in the age group 65-74, there is a 2.3 times greater

chance of scoring NCD-mild compared with patients 75 years old or more (reference class to age group) (OR=2.291, %CI:1.001-5.244).

Years of the study are significant with respect to NCD, based on multivariate analysis. Patients with 0-2 years of education have about 10 times greater chance of scoring NCD-mild, 44 times greater chance of scoring MCD-major, and 7.3 greater chance of scoring PCD (OR=10.783, %CI=2.083-55.812, p-value=0.005; OR=44.435, %CI=6.646-297.099, p-value<0.001; OR=7.339, %CI=1.934-27.856, p-value=0.003, respectively).

Relative to comorbidities, special attention is necessary regarding GID. These patients have about 1.9 times greater chance of scoring PCD, compared to NCD-normal (OR=1.905, CI=(1.121-3.236, p-value=0.017).

Another variable that presents statistical significance with respect to cognitive performance is ADL. For the latter, there is a 58 times greater chance of scoring NCD-major and 9.5 time greater chance to score PCD, relative the NCD-normal performance (OR=58.117, CI=5.851-577.243, p-value<0.001; OR=9.562, CI=1.170-78.116, p-value=0.035).

Relative to the performance of the statistical model in multivariate analysis, it is necessary to identify the important variables to predict the model. The-2log likelihood decreases relative to the model only with the constant (from 826.561 to 679.292) but the model significantly improved (p<0.05) with the introduction of predictive variables. Goodness-of-fit tests the adjustment of the variables to the model, if p>0.05 then the variables fits the model well. In this model, the Goodness-of-fit (Deviance 505.975, $df_{(663)}$, p-value=1.000) means that the variable fits to the model. Table 19 shows the variables that contributed with statistical significance to final model in this statistical analysis.

Table 19 Internal model of the multivariate analyses of the pcb-Cohort for NCD

Effect	Model Fitting Criteria			Likelihood Ratio Tests		
	AIC of Reduced Model	BIC of Reduced Model	-2 Log Likelihood of Reduced Model	Chi-Square	df	Sig.
Intercept	763.292	940.973	679.292[a]	.000	0	.
APOEε2 non carrier	760.923	925.912	682.923	3.631	3	0.304
APOEε4 carrier	771.085	936.074	693.085	13.793	3	**0.003**
Female	802.271	967.260	724.271	44.979	3	**<0.001**
Age Group	762.026	914.323	690.026	10.734	6	0.097
Literacy	774.499	926.796	702.499	23.206	6	**0.001**
HTA	758.682	923.671	680.682	1.390	3	0.708
OA	762.461	927.450	684.461	5.169	3	0.160
GID	764.159	929.147	686.159	6.866	3	0.076
DM	760.017	925.006	682.017	2.725	3	0.436
NEURO	766.077	931.066	688.077	8.785	3	**0.032**
ADL	780.865	945.853	702.865	23.572	3	**0.000**

Abbreviation: HYP-Hypertension arterial; OA-Osteoarthicular disease; GID-Gastrointestinal Disease; DM-Diabetes Mellitus; NEURO-Neuropathologies; ADL-Basic Activities daily of Life. The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

The model used for the multivariate analysis is a good fit conforming to the variables as previously described. The variables that contribute significantly to the final model are those identified in bold (Table 19). The *APOE* allele carriers, age group, literacy, ADL, IADL and NEURO contribute significantly to the cognitive performance of individuals. The chi-square test is the difference in-2 log-likelihoods between the final model and a reduced model.

Results

4.2 Depression Evaluation of the pcb-Cohort

4.2 Depression Evaluation of the pcb-Cohort

Depression affects many individuals in the pcb-Cohort. As described in the methods section the GDS (Geriatric Depression Scale) was applied to participants. The prevalence of depression, based on the clinical history, is 32% (N=182). Depression prevalence based on the GDS15 questionnaire (174) is 30.6% (Figure 7). However, when GDS4Lit (GDS4 based on the literature [197]) was applied, unexpectedly, only 46 (8.1%) patients obtained scores consistent with the absence of a depressive status and 522 scored above 2 points, that is a score consistent with possible cases of depression. These results are represented in figure 7.

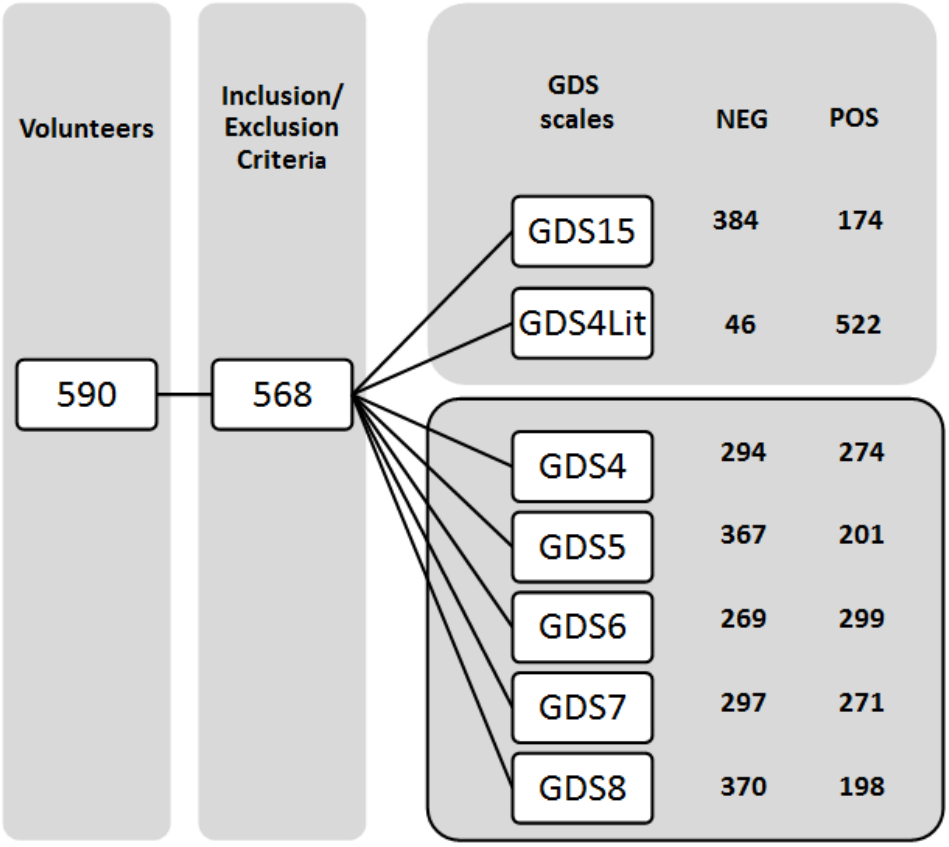


Figure 7 GDS scales applied to the pcb-Cohort
Of the 590 volunteers, 568 were within the inclusion criteria. Distinct analyses of the GDS were applied to the study population as explained in the materials and methods. The number of individuals scoring negative or positive for depression changed with respect to the analysis implemented.

4.2.1 Comparing the Geriatric Depressive Scale (GDS) with 15 Items and GDS with 4 Items as Reported in the Literature

In the pcb-Cohort, applying GDS15 and GDS4Lit resulted in significantly different numbers of potentially depressed patients (Figure 7), 174 and 522 positive cases respectively. Given this difference each of the questions of GDS15 was evaluated independently. That is, each question was scored as positive if answered in a manner consistent with depression. The percentage was then calculated as a function of the total number of patients with depression, as determined by the GDS15 (N=174) (Figure 7). There is a marked difference in the top responses denoting positivity for depressive symptoms when comparing the GDS15 with the short version GDS4Lit. In other words, the top responses denoting positivity for depression to GDS4Lit are not the same as the top ones for GDS15 (Figure 8).

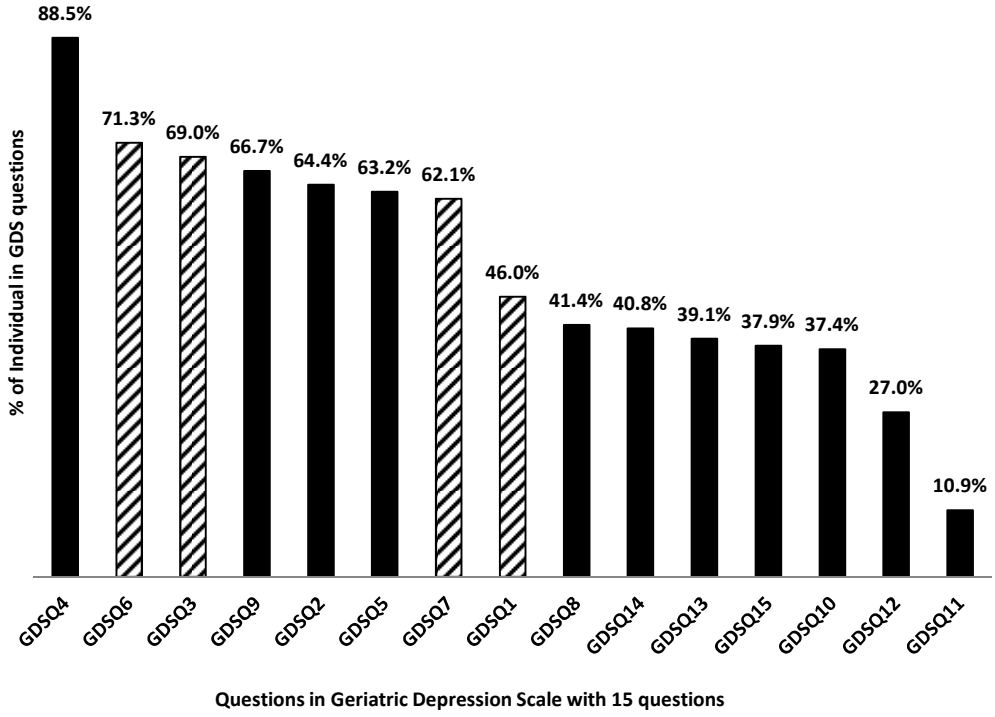


Figure 8 Frequency of answers consistent with depression in the GDS15 for the pcb-Cohort
The number in front of GDS corresponds to the number of the question in the original GDS15 questionnaire (see methods). Stripped columns represent the four questions in the short version of GDS4Lit described in the literature. That is questions: GDSQ1, GDSQ3, GDSQ6 and GDSQ7 [186]. The percentage referred is based in individuals scoring in a pattern consistent with depression for each of the questions. Values are shown as a percentage of the total number of individuals scoring positive for Depression N=174 (GDS15).

4.2.2 Applying Alternative Shorter GDS Versions

Since there was a significant discrepancy in the number of possible cases of depression using GDS4Lit compared to GDS15, other shorter versions of the GDS were evaluated. Thus, in the shorter versions, and respecting the order of most frequent questions where “yes” or “no” response denoted an association with depression (Figure 8), GDS scales with fewer questions were considered. The number of questions included was progressively increased, from the top four to the top eight. The top eight questions considered had around 50% depressed people (N=174) responding in a pattern consistent with depression (Figure 8). The top 4 questions in GDS4 (questions 4, 6, 3 and 9) most answered are different from those used in the previous publication GDS4Lit (these questions are: 6, 3, 7 and 1). For the shorter versions tested, the top five questions included in the GDS5 (questions 4, 6, 3, 9 and 2), the top six questions in GDS6 (questions 4, 6, 3, 9, 2 and 5), the top seven questions in GDS7 (questions 4, 6, 3, 9, 2, 5 and 7) and the top eight in the GDS8 (questions 4, 6, 3, 9, 2, 5, 7 and 1).

4.2.3 Determining cut-off Points for the Shorter GDS Versions

Cut-off points for each of the scales tested were determined, as explained in the methodology (3.11.2.3). For each point, sensitivity and specificity is identified. The best cut-off point is the one with the best correlation between these two parameters. The ROC curve and the coordinates of the curves are represented in figure 9. These coordinates are expressed in table 20.

.

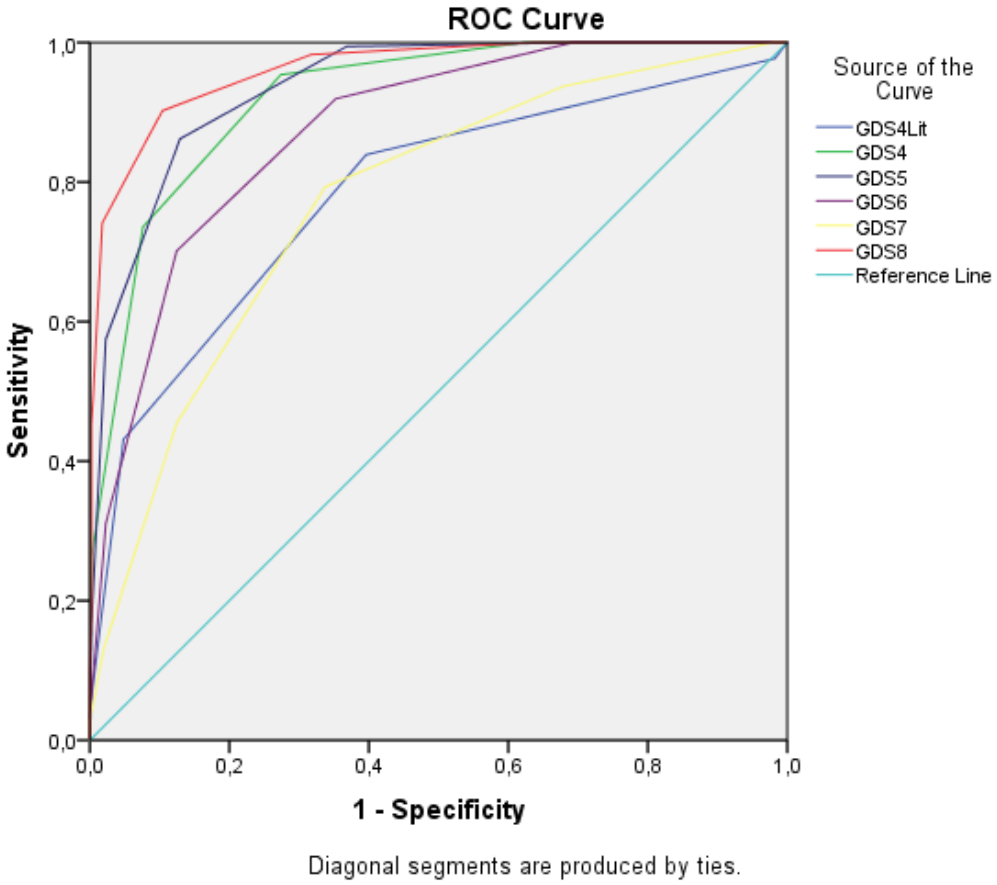


Figure 9 ROC curves for shorter GDS scales

The number of questions in each of the different GDS analyses is as previously explained and based on the top incorrect answers of the GDS15. The AUC (Area Under Curve) for GDS8 is 0.961 (CI (Confidential Interval) 95% 0.946-0.976); for GDS7 it is 0.772 (95%CI 0.731-0.813); for GDS6 it is 0.974 (CI 95% 0.845 – 0.903); for GDS5 it is 0.937 (CI 95% 0.918-0.956); for GDS4 it is 0.922 (95%CI 0.900-0.944); and for GDS4Lit it is 0.782 (95%CI 0.739-0.826). The curves with the best discriminating power are GDS8 and GDS6. The null hypothesis: true area=0.5.

Looking at the coordinates that are shown in table 20 one can see that a patient with a positive result presents a result consistent with "depression" if the cut-off points are those highlighted in the table (Table 20). Therefore, the best cut offs for the different short versions are: GDS8 ≥ 3; GDS7 ≥ 4; GDS6 ≥ 3; GDS5 ≥ 3; GDS4 ≥ 2.

Table 20 ROC curve to determine cut-off points for the shorter GDS versions

Short Version	Positive if Greater Than or Equal To	Sensitivity	Specificity
GDS8	-1.0	1.000	0.000
	0.5	1.000	0.365
	1.5	0.983	0.683
	2.5	**0.902**	**0.896**
	3.5	0.741	0.982
	4.5	0.454	0.997
	5.5	0.195	0.997
	6.5	0.098	1.000
	7.5	0.029	1.000
	9.0	0.000	1.000
GDS7	0.0	1.000	0.000
	1.5	1.000	0.020
	2.5	0.937	0.322
	3.5	**0.793**	**0.662**
	4.5	0.454	0.876
	5.5	0.132	0.980
	6.5	0.029	1.000
	8.0	0.000	1.000
GDS6	-1.0	1.000	0.000
	0.50	1.000	0.003
	1.5	1.000	0.307
	2.5	**0.920**	**0.647**
	3.5	0.701	0.876
	4.5	0.310	0.977
	5.5	0.034	1.000
	7.0	0.000	1.000
GDS5	-1.0	1.000	0.000
	0.5	1.000	0.302
	1.0	0.994	0.632
	2.5	**0.862**	**0.871**
	3.5	0.575	0.977
	4.5	0.167	0.997
	6.0	0.000	1.000
GDS4	-1.0	1.000	0.000
	0.5	1.000	0.376
	1.5	**0.954**	**0.726**
	2.5	0.736	0.924
	3.5	0.264	0.997
	5.0	0.000	1.000
GDS4Lit	-1.0	1.000	0.000
	0.5	0.977	0.018
	1.5	**0.839**	**0.604**
	2.5	0.431	0.952
	3.5	0.063	0.997
	5.0	0.000	1.000

The test result variable(s): GDS8, GDS7, GDS6, GDS5, GDS4, GDS 4Lit question has at least one tie between the positive actual state group and the negative actual state group. The smallest cut-off value is the minimum observed test value minus 1. And the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

Since we have the questions that best indicate depression in the study population, it follows that the cut-off points for the new scales here proposed should be identified (Table 20). As explained in the methods, the ROC Curve provides important information on the accuracy of the scales. The area under the curve shows

that the use of the test is better than chance alone but, in addition, the coordinates of the curve are very useful because they provide guidelines to help determine the best cut-off points for the shorter versions proposed for the pcb-Cohort population. Along with the curve, the coordinate points of the curve are also available in the statistical program. For each point, one has the sensitivity and specificity. The best cut-off point is the one with the best correlation between these two parameters.

4.2.4 Evaluating the Predictive Values to Shorter GDS Versions

Subsequently the following question was asked: Given that the diagnostic test with our proposed short versions showed a positive (or negative) result, what is the probability that the patient is putatively positive or negative for depression? This test attribute is known as Predictive Value (PV) and may be positive (PPV) or negative (NPV), and it is determined by the interaction of three variables: the sensitivity and specificity of the test and the prevalence of the disease in the study group [177,198]. PPV is the proportion of patients (with disease) among all the individuals with a positive result by the test. NPV is the proportion of healthy (without the disease) individuals among the negative ones. These tests (PPV and NPV) are important to show the validity of the proposed shorter versions.

As explained above shorter versions with specific cut-off points were proposed. These results were compared with the gold standard, the GDS15. PPV is calculated based on patients who have both positive tests divided by the total positive of the gold standard GDS15 (N=174). NPV is calculated based on the patients without depression in the proposed test, divided by the total of negative in the gold standard test.

Table 21 shows the correlation between the positive and negative results of the shorter GDS versions compared to GDS15, the calculated value of positive and negative predictive values for all versions is also shown. All proposed shorter versions present a statistically significant correlation with GDS15, except for the version with four questions already described in the literature (GDS4Lit).

Table 21 Measure of positive predictive value and negative predictive value

Short Versions		N%	GDS15		p-value	S	SP	PPV	NPV
			GDS15- N=374 69.4%	GDS15+ N=174 30.6%					
GDS8	GDS8-	370 65.1%	353[a] 89.6%	17[b] 9.8%	**0.001**	90.2	89.6	79%	95%
	GDS8+	198 34.9%	41[a] 10.4%	157[b] 90.2%					
GDS7	GDS7-	297 52.3%	261[a] 66.2%	36[b] 20.7%	**0.001**	79.3	66.2	51%	88%
	GDS7+	271 47.7%	133[a] 33.8%	138[b] 79.3%					
GDS6	GDS6-	269 47.4%	255[a] 64.7%	14[b] 8.0%	**<0.001**	92	64.7	54%	95%
	GDS6+	299 52.6%	139[a] 35.3%	160[b] 92.0%					
GDS5	GDS5-	367 64.6%	343[a] 87.1%	24[b] 13.8%	**<0.001**	86.2	87.1	75%	93%
	GDS5+	201 35.4%	51[a] 12.9%	150[b] 86.2%					
GDS4	GDS4-	294 51.8%	286[a] 72.6%	8[b] 4.6%	**<0.001**	95.4	72.6	61%	97%
	GDS4+	274 48.2%	108[a] 27.4%	166[b] 95.4%					
GDS4Lit	GDS4Lit-	46 8.1%	16[a] 4.1%	30[b] 17.2%	0.070	83.9	60.4	28%	35%
	GDS4Lit+	522 91.9%	378[a] 95.9%	144 82.8%					

Abbreviation: GDS: Geriatric Depression Scale; -: negative test; +: positive test; GDS8 is short version with eight questions; GDS7 is short version with seven questions; GDS6 is short version with six questions; GDS5 is short version with five questions; GDS4 is short version with four questions; GDS4Lit is short version with four questions in literature. S-Sensibility; SP-Specificity; PPV-Positive predictive value; NPV-Negative predictive value; Statistical test: *χ2-Chi square test. Superscripts letters: [a,b] the same subscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, p-value<0.05.

4.2.5 Depression Characterization in the pcb-Cohort as a Function of Different GDS Versions

Having established the shorter GDS versions, a comparison of the socio-demographic, clinical and cognitive characteristics of all versions was carried out. One of the ways to validate the veracity of the information proposed by the short versions is to verify if the correlations observed with the GDS15 gold standard are also observed with the proposed short GDS versions.

4.2.5.1 Sociodemographic characterization

Tables 22 and 23 show correlations of sociodemographic characteristics compared to GDS15 or the different GDS versions: 4Lit, 4, 5, 6, 7 and 8 questions. There is a statistically significant correlation with age (for GDS5), gender (for GDS5, 6, 7, 8 and 15), marital status (for GDS15), monthly family income (for GDS8 and 15), living arrangement (all GDS cut offs tested including GDS4Lit), level of education (for GDS8 and 15) and professional status (for GDS4, 5, 6, 7, 8 and 15). Depressive status is highest in women, individuals living alone, in lower monthly income situations (less than 1 minimum wage) and with lower literacy levels. It is observed that the scale that presents results most like GDS15 is the short version with 8 questions. It is also evident that the GDS4Lit does not effectively characterize the pcb-Cohort population, when compared to the GDS15.

Table 22 Correlation of sociodemographic characteristics with GDS15

Sociodemographic Characteristics	N=568	GDS		p-value
		GDS15- 394(69.7%)	GDS15+ 174 (30.3%)	
Gender				
Male	163 (28.7%)	128 [a] (32.5%)	35 [b] (20.1%)	**0.003**
Female	405 (71.3%)	266 [a] (67.5%)	139 [b] (79.9%)	
Age group				
50-64 years old	202 (35.6%)	148 [a] (37.6%)	54 [a] (31.0%)	
65-74 years old	229 (40.3%)	159 [a] (40.4%)	70 [a] (40.2%)	0.160
≥ 75 years old	137 (24.1%)	87 [a] (22.1%)	50 [a] (28.7%)	
Marital Status				
Living with the partner	400 (70.4%)	291 [a] (73.9%)	109 [b] (62.6%)	**0.007**
Others situations	168 (29.6%)	103 [a] (26.1%)	65 [b] (37.4%)	
Living Arrangement				
Alone	96 (16.9%)	56 [a] (14.2%)	40 [b] (23.0%)	**0.010**
Accompanied	472 (83.1%)	338 [a] (85.8%)	134 [b] (77.0%)	
Professional Status				
Active	176[a] (31%)	125 [a] (37.1%)	51 [a] (29.3%)	
Reformed	362 [a] (63.7 %)	254 [a] (64.2%)	108 [b] (62.1%)	**0.010**
Desemployed	31 [a] (5.3)	16 [a] (4.1%)	15[b] (8.6%)	
Monthly Family Income				
≤1 MW	176 (31.0%)	106 [a] (26.9%)	70 [b] (40.2%)	**0.002**
>1 MW	392 (69.0%)	288 [a] (73.1%)	104 [b] (59.8%)	
Literacy				
0-2 years of Literacy	51 (9.0%)	23 [a] (5.8%)	28 [b] (16.1%)	
3-6 years of Literacy	402 (70.8%)	282 [a] (71.6%)	120 [a] (69.0%)	**<0.001**
≥7 years of Literacy	115 (20.2%)	89 [a] (22.6%)	26 [b] (14.9%)	

Abbreviation: GDS: Geriatric Depression Scale; -: negative test; +: positive test; Statistical test: χ^2 (Chi Square). MW=Minimum Wage; Superscripts letters: [a,b] the same subscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, p-value<0.05.

Table 23 Sociodemographic characteristics and shorter GDS versions

Sociodemographic characteristics	N	GDS4Lit			GDS4			GDS5			GDS6			GDS7			GDS8			GDS15		
		GDS4Lit-	GDS4Lit+	p-value	GDS4-	GDS4+	p-value	GDS5-	GDS5+	p-value	GDS6-	GDS6+	p-value	GDS7-	GDS7+	p-value	GDS8-	GDS8+	p-value	GDS15-	GDS15+	p-value
Gender																						
Male	163	11[a]	152[a]	0.454	102[a]	61[b]	**0.001**	121[a]	42[b]	**0.002**	97[a]	66[b]	**<0.001**	101[a]	62[b]	**0.003**	123[a]	40[b]	**0.001**	128[a]	35[b]	**0.003**
	28.7%	23.9%	29.1%		34.7%	22.3%		33.0%	20.9%		36.1%	22.1%		34.0%	22.9%		33.2%	20.2%		32.5%	20.1%	
Female	405	35[a]	370		192[a]	213[b]		246[a]	159[b]		172[a]	233[b]		196[a]	209[b]		247[a]	158[b]		266[a]	139[b]	
	71.3%	76.1%	[a]70.9%		65.3%	77.7%		67.0%	79.1%		63.9%	77.9%		66.0%	77.1%		66.8%	79.8%		67.5%	79.9%	
Age																						
Age 50-64	202	17[a]	185[a]	0.883	109[a]	93[a]	0.618	143[a]	59[a]	0.065	101[a]	101[a]	0.627	113[a]	89[b]	0.389	140[a]	62[a]	0.293	148[a]	54[a]	0.160
	35.6%	37.0%	35.4%		37.1%	33.9%		39.0%	29.4%		37.5%	33.8%		38.0%	32.8%		37.8%	31.3%		37.6%	31.0%	
65-74	229	17[a]	212[a]		113[a]	116[a]		138[a]	91[a]		104[a]	125[a]		113[a]	116[a]		145[a]	84[a]		159[a]	70[a]	
	40.3%	37.0%	40.6%		38.4%	42.3%		37.6%	45.3%		38.7%	41.8%		38.0%	42.8%		39.2%	42.4%		40.4%	40.2%	
>= 75	137	12[a]	125[a]		72[a]	65[a]		86[a]	51[a]		64[a]	73[a]		71[a]	66[a]		85[a]	52[a]		87[a]	50[a]	
	24.1%	26.1%	23.9%		24.5%	23.7%		23.4%	25.4%		23.8%	24.4%		23.9%	24.4%		23.0%	26.3%		22.1%	28.7%	
Marital Status																						
Living with the partner	400	32[a]	368[a]	0.455	209[a]	191[a]	0.171	264[a]	136[a]	0.071	194[a]	206[a]	0.086	210[a]	190[a]	0.381	272[a]	128[a]	0.103	291[a]	109[a]	0.086
	70.4%	69.6%	70.5%		71.1%	69.7%		71.9%	67.7%		72.1%	68.9%		70.7%	70.1%		73.5%	64.6%		73.9%	62.6%	
Others Situations	168	14[a]	154[a]		85[a]	83[a]		103[a]	65[a]		75[a]	93[a]		87[a]	81[a]		98[a]	70[a]		103[a]	65[a]	
	29.6%	30.4%	29.5%		28.9%	30.3%		28.1%	32.3%		27.9%	31.1%		29.3%	29.9%		26.5%	35.4%		26.1%	37.4%	
Living Arrangement																						
Alone	96	11[a]	85[b]	**0.025**	45[a]	51[b]	**0.010**	56[a]	40[b]	**0.009**	40[a]	56[b]	**0.002**	47[a]	49[b]	**0.004**	52[a]	44	**0.001**	56[a]	40[b]	**0.002**
	16.9%	23.9%	16.3%		15.3%	18.6%		15.3%	19.9%		14.9%	18.7%		15.8%	222[b]		14.1%	[b]22.2%		14.2%	23.0%	
Accompanied	472	35[a]	437[b]		249[a]	223[b]		311	161[b]		229[a]	243[b]		250[a]	81.9%		318[a]	154[b]		338[a]	134[b]	
	83.1%	76.1%	83.7%		84.7%	81.4%		[a]84.7%	80.1%		85.1%	81.3%		84.2%			85.9%	77.8%		85.8%	77.0%	
Professional Status																						
Active	176	18[a]	158[a]	0.096	94[a]	82[a]	**<0.001**	125[a]	51[b]	**0.001**	89[a]	87[b]	**<0.001**	97[a]	79[b]	**0.026**	120[a]	56[b]	**<0.001**	125[a]	51[b]	**<0.001**
	31.0%	39.1%	30.3%		32.0%	29.9%		34.1%	25.4%		33.1%	29.1%		32.7%	29.2%		32.4%	28.3%		31.7%	29.3%	
Reformed	361	26[a]	335[a]		189[a]	172[a]		225[a]	136[a]		171[a]	190[a]		187[a]	174[b]		235[a]	126[b]		253[a]	108[b]	
	63.6%	56.5%	64.2%		64.3%	62.8%		61.3%	67.7%		63.6%	63.5%		63.0%	64.2%		63.5%	63.6%		64.2%	62.1%	
Unemployed	31	2[a]	29[a]		11[a]	20[b]		17[a]	14[b]		9[a]	22[b]		13[a]	18[b]		15[a]	16[b]		16[a]	15[b]	
	5.5%	4.3%	5.6%		3.7%	7.3%		4.6%	7.0%		3.3%	7.4%		4.4%	6.6%		4.1%	8.1%		4.1%	8.6%	
Monthly wage																						
<= 1 Minimum Wage	176	21[a]	155[a]	0.894	77[a]	99[a]	0.719	100[a]	76[a]	0.286	66[a]	110[a]	0.401	76[a]	100[a]	0.876	97[a]	79[b]	**0.027**	106[a]	70[b]	**0.007**
	31.0%	45.7%	29.7%		26.2%	36.1%		27.2%	37.8%		24.5%	36.8%		25.6%	36.9%		26.2%	39.9%		26.9%	40.2%	
>1 Minimum Wage	392	25[a]	367[a]		217[a]	175[a]		267[a]	125[a]		203[a]	189[a]		221[a]	171[a]		273[a]	119[b]		288[a]	104[b]	
	69.0%	54.3%	70.3%		73.8%	63.9%		72.8%	62.2%		75.5%	63.2%		74.4%	63.1%		73.8%	60.1%		73.1%	59.8%	
Years of Study																						
0-2 years of Literacy	51	8[a]	43[a]	0.186	16[a]	35[a]	0.293	26[a]	25[a]	0.158	16[a]	35[a]	0.220	26[a]	25[a]	0.474	25[a]	26[b]	**0.013**	23[a]	28[b]	**0.010**
	9.0%	17.4%	8.2%		5.4%	12.8%		7.1%	12.4%		5.9%	11.7%		8.8%	9.2%		6.8%	13.1%		5.8%	16.1%	
3-6 years of Literacy	402	28[a]	374[a]		198[a]	204[a]		251[a]	151[a]		182[a]	220[a]		198[a]	204[a]		252[a]	150[b]		282[a]	120[b]	
	70.8%	60.9%	71.6%		67.3%	74.5%		68.4%	75.1%		67.7%	73.6%		66.7%	75.3%		68.1%	75.8%		71.6%	69.0%	
≥ 7 years of Literacy	115	10[a]	105[a]		80[a]	35[a]		90[a]	25[a]		71[a]	44[a]		73[a]	42[a]		93[a]	22[b]		89[a]	26[b]	
	20.2%	21.7%	20.1%		27.2%	12.8%		24.5%	12.4%		26.4%	14.7%		24.6%	15.5%		25.1%	11.1%		22.6%	14.9%	

4.2.5.2 Clinical evaluation of pcb-Cohort patients based on shorter GDS versions

As with the sociodemographic characteristics, the clinical characteristics were correlated with GDS15, as well as with the shorter GDS versions (Table 24).

There are statistical significant correlations with GDS15+ and patients with OA, that have a diagnosis of DEP and as well as being diagnosed with GID. Regarding the shorter versions GDS6, GDS7, GDS8 all have the same correlations for comorbidities as those seen for GDS15. The GDS4 and GDS5 versions, in addition to the same correlations already mentioned above, include a correlation with HYP. However, the GDS4Lit version does not reveal any correlation with the comorbidities tested for the pcb-Cohort.

Hypertensive patients do not present a positive correlation with the scales studied here, except in GDS4 and 5. Patients with DYP, CVD, GUD, DM, RESP and NEURO do not exhibit statistically significant correlations with any of the GDS versions tested. As already mentioned above, GDS4Lit fails to reveal any significant correlations.

Taken together one can deduce that the worst performer in the pcb-Cohort is GDS4Lit and that the shorter versions GDS4 and 5 duplicate the results obtained with GDS15. The remaining shorter versions GDA 6, 7 and 8 behave in a manner like that seen for GDS15.

Table 24 Correlation of comorbidities and shorter GDS versions

Comorbidities		GDS4Lit			GDS4			GDS5			GDS6			GDS7			GDS8			GDS15		
		GDS4Lit-	GDS4Lit+	*p*	GDS4-	GDS4+	*p*	GDS5-	GDS5+	*p*	GDS6-	GDS6+	*p*	GDS7-	GDS7+	*p*	GDS8-	GDS8+	*p*	GDS15-	GDS15+	*p*
HYP	N=351	27[a]	324[a]	0.652	167[a]	184[b]	**0.011**	216[a]	135[a]	**0.051**	156[a]	195[a]	0.077	176[a]	175[a]	0.193	224[a]	127[a]	0.400	241[a]	110[a]	0.643
		58,7%	62,1%		56,8%	67,2%		58,9%	67,2%		58,0%	65,2%		59,3%	64,6%		60,5%	64,1%		61,2%	63,2%	
DYS	N=333	27[a]	306[a]	0.992	172[a]	161[a]	0.951	216[a]	117[a]	0.881	154[a]	179[a]	0.527	172[a]	161[a]	0.717	222[a]	111[a]	0.364	233[a]	100[a]	0.710
		58,7%	58,6%		58,5%	58,8%		58,9%	58,2%		57,2%	59,9%		57,9%	59,4%		60,0%	56,1%		59,1%	57,5%	
OA	N=305	24[a]	281[a]	0.829	139[a]	166[b]	**<0.001**	172[a]	133[b]	**<0.001**	121[a]	184[b]	**<0.001**	138[a]	167[b]	**<0.001**	179[a]	126[b]	**0.001**	199[a]	106[b]	**0.022**
		52,2%	53,8%		47,3%	60,6%		46,9%	66,2%		45,0%	61,5%		46,5%	61,6%		48,4%	63,6%		50,5%	60,9%	
CV	N=302	23[a]	279[a]	0.653	161[a]	141[a]	0.431	195[a]	107[a]	0.982	144[a]	158[a]	0.870	162[a]	140[a]	0.491	205[a]	97[a]	0.144	219[a]	83[a]	0.083
		50,0%	53,4%		54,8%	51,5%		53,1%	53,2%		53,5%	52,8%		54,5%	51,7%		55,4%	49,0%		55,6%	47,7%	
DEP	N=182	17[a]	165[a]	0.456	75[a]	107[b]	**<0.001***	102[a]	80[b]	**0.003**	67[a]	115[b]	**0.001**	76[a]	106[b]	**0.001**	102[a]	80[b]	**0.002**	108[a]	74[a]	**<0.001**
		37,0%	31,6%		25,5%	39,1%		27,8%	39,8%		24,9%	38,5%		25,6%	39,1%		27,6%	40,4%		27,4%	42,5%	
GID	N=151	11[a]	140[a]	0.669	62[a]	89[b]	**0.002**	82[a]	69[b]	**0.002**	59[a]	92[b]	**0.017**	65[a]	86[b]	**0.008**	82[a]	69[b]	**0.001**	93[a]	58[a]	**0.016**
		23,9%	26,8%		21,1%	32,5%		22,3%	34,3%		21,9%	30,8%		21,9%	31,7%		22,2%	34,8%		23,6%	33,3%	
GUD	N=122	11[a]	111[a]	0.675	70[a]	52[a]	0.161	80[a]	42[a]	0.802	64[a]	58[a]	0.203	67[a]	55[a]	0.512	82[a]	40[a]	0.588	88[a]	34[a]	0.455
		23,9%	21,3%		23,8%	19,0%		21,8%	20,9%		23,8%	19,4%		22,6%	20,3%		22,2%	20,2%		22,3%	19,5%	
DM	N=115	10[a]	105[a]	0.793	58[a]	57[a]	0.750	71[a]	44[a]	0.471	54[a]	61[a]	0.923	63[a]	52[a]	0.549	71[a]	44[a]	0.391	78[a]	37[a]	0.688
		21,7%	20,1%		19,7%	20,8%		19,3%	21,9%		20,1%	20,4%		21,2%	19,2%		19,2%	22,2%		19,8%	21,3%	
RESP	N=93	9[a]	84[a]	0.542	43[a]	50[a]	0.244	56[a]	37[a]	0.332	38[a]	55[a]	0.170	43[a]	50[a]	0.201	55[a]	38[a]	0.184	59[a]	34[a]	0.175
		19,6%	16,1%		14,6%	18,2%		15,3%	18,4%		14,1%	18,4%		14,5%	18,5%		14,9%	19,2%		15,0%	19,5%	
NEURO	N=22	3[a]	19[a]	0.332	11[a]	11[a]	0.866	15[a]	7	0.721	10[a]	12	0.855	11[a]	11[a]	0.826	13[a]	9[a]	0.544	14[a]	8	0.552
		6,5%	3,6%		3,7%	4,0%		4,1%	3,5%		3,7%	4,0%		3,7%	4,1%		3,5%	4,5%		3,6%	4,6%	

Abbreviations: HYP-Hypertension Arterial; DYS-Dyslipidaemia; OA-Osteoarthicular Disease; CVD-Cardiovascular Disease; DEP-Depression; GID-Gastrointestinal Disease; GUD-Genitourinary Disease; DM-Diabetes Mellitus; RESP-Respiratory Disease; NEURO-Neurologic Disease. SD= Standard Deviation; GDS-Geriatric Depression State; GDS4Lit- 4 questions in questionnaire in the literature; GDS4-4 questions more frequent in pcb-Cohort; GDS5-5 more frequent questions in pcb-Cohort; GDS6-6 more frequent questions in pcb-Cohort; GDS7-7 more frequent questions in pcb-Cohort; GDS8-8 more frequent questions in pcb-Cohort. (-)patients with GDS negative. (+) patients with GDS positive.

NOTE:

1.Comorbidities studied are described in [2];

2. Data presented as N (%) and % is expressed as a function of the total in each of the GDS groups or mean ± standard deviation;

3. In bold and underline p-value < 0.05;

4.Statistical test used are: $\chi 2$ = Chi square test; [a,b] The same subscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level.

4.2.5.3 Correlation of shorter GDS versions with cognitive performance

Since forgetfulness correlates with depression and since depression has, in other studies, been correlated with the poor cognitive performance [15], the present study evaluated how the shorter GDS versions and GDS15 behave relative to cognitive performance. Cognitive assessment is based on the CDR and MMSE and the results are presented in table 25. There is a good significant correlation with almost all the shorter GDS versions tested, except for GDS4Lit with respect to the CDR results. Results are similar when the MMSE data is considered, although in the latter GDS7 exhibits a lower level of significance with a p-value=0.074. To summarize there is a high correlation between low cognitive performance and positive GDS scores, even when fewer questions are considered.

Table 25 Correlation of shorter GDS versions and cognitive evaluation based on CDR and MMSE

GDS version	N (%) 568	CDR			*p-value*	MMSE		*p-value*
		CDR=0 N=301	CDR=0.5 N=199	CDR≥1 N=68		MMSE- N=436	MMSE+ N=132	
GDS15	GDS15- 394 69.4%	250[a] 83.1%	112[b] 56.3%	32[b] 47.1%	**<0.001**	370[a] 72.0%	24[b] 44.4%	**<0.001**
	GDS15+ 174 30.6%	51[a] 16.9%	87[b] 43.7%	36[b] 52.9%		144[a] 28.0%	30[b] 55.6%	
GDS8	GDS8- 370 65.1%	231[a] 76.7%	105[b] 52.8%	34[b] 50.0%	**<0.001**	344[a] 66.9%	26[b] 48.1%	**0.006**
	GDS8+ 198 34.9%	70[a] 23.3%	94[b] 47.2%	34[b] 50.0%		170[a] 33.1%	28[b] 51.9%	
GDS7	GDS7- 297 52.3%	182[a] 60.5%	90[b] 45.2%	25[b] 36.8%	**<0.001**	275[a] 53.5%	22[a] 40.7%	*0.074*
	GDS7+ 271 47.7%	119[a] 39.5%	109[b] 54.8%	43[b] 63.2%		239[a] 46.5%	32[a] 59.3%	
GDS6	GDS6- 269 47.4%	169[a] 56.1%	79[b] 39.7%	21[b] 30.9%	**<0.001**	251[a] 48.8%	18[b] 33.3%	**0.030**
	GDS6+ 299 52.6%	132[a] 43.9%	120[b] 60.3%	47[b] 69.1%		263[a] 51.2%	36[b] 66.7%	
GDS5	GDS5- 367 64.6%	229[a] 76.1%	106[b] 53.3%	32[b] 47.1%	**<0.001**	342[a] 66.5%	25[b] 46.3%	**0.003**
	GDS5+ 201 35.4%	72[a] 23.9%	93[b] 46.7%	36[b] 52.9%		172[a] 33.5%	29[b] 53.7%	
GDS4	GDS4- 294 51.8%	190[a] 63.1%	80[b] 40.2%	24[b] 35.3%	**<0.001**	275[a] 53.5%	19[b] 35.2%	**0.010**
	GDS4+ 274 48.2%	111[a] 36.9%	119[b] 59.8%	44[b] 64.7%		239[a] 46.5%	35[b] 64.8%	
GDS4Lit	GDS4Lit- 46 8.1%	19[a] 6.3%	20[a] 10.1%	7[a] 10.3%	0.253	40[a] 7.8%	6[a] 11.1%	0.394
	GDS4Lit+ 522 91.9%	282[a] 93.7%	179[a] 89.9%	61[a] 89.7%		474[a] 92.2%	48[a] 88.9%	

Abbreviations: GDS: Geriatric Depression Scale; -: negative test; +: positive test; GDS4Lit- 4 questions in questionnaire in the literature; GDS4-4 questions more frequent in pcb-Cohort; GDS5-5 more frequent questions in pcb-Cohort; GDS6-6 more frequent questions in pcb-Cohort; GDS7-7 more frequent questions in pcb-Cohort; GDS8-8 more frequent questions in pcb-Cohort; Statistical test: χ^2 (Chi Square). Superscripts letters: [a.b] the same subscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value<0.05.

4.2.5.4 APOE Genotyping and shorter GDS versions

Subsequently the different GDS versions were compared to the *APOE* genotype (Table 26). This is particularly relevant as *APOE* genotype has been reported to be the highest risk factor for dementia, in particular AD [57,192,199] and given that GDS has a strong correlation with poor cognitive performance [132] this analysis was carried out.

Of the different GDS cut-offs here tested the GDS15 and GDS8 gave the best correlation with the *APOE E4*.

The proportion of patients who are GDS15+ is higher inε4 carriers than non-carriers, with statistical significance (p-value=0.041). Similar results are observed for the GD8 version (p-value=0.004). The other GDS versions tested have no significant statistical relationship with any of the *APOE* alleles.

Table 26 Correlation of shorter GDS versions and APOE genotype

GDS Versions	N (%)	*APOE*								
		Non ε2 carriers N=470	ε2 carriers N=38	p-value	Non ε3 carriers N=14	ε3 carriers N=494	p-value	Non ε4 carriers N=412	ε4 carriers N=96	p-value
GDS15	GDS15- 351 69.1%	323[a] 68.7%	28[a] 73.7%	0.524	9[a] 64.3%	342[a] 69.2%	0.693	293[a] 71.1%	58[b] 60.4%	**0.041**
	GDS15+ 157 30.9%	147[a] 31.3%	10[a] 26.3%		5[a] 35.7%	152[a] 30.8%		119[a] 28.9%	38[b] 39.6%	
GDS8	GDS8- 333 65.6%	308[a] 65.5%	25[a] 65.8%	0.974	10[a] 71.4%	323[a] 65.4%	0.639	282[a] 68.4%	51[b] 53.1%	**0.004**
	GDS8+ 175 34.4%	162[a] 34.5%	13[a] 34.2%		4[a] 28.6%	171[a] 34.6%		130[a] 31.6%	45[b] 46.9%	
GDS7	GDS7- 273 53.7%	247[a] 52.6%	26[a] 68.4%	0.059	10[a] 71.4%	263[a] 53.2%	0.178	226[a] 54.9%	47[a] 49.0%	0.297
	GDS7+ 235 46.3%	223[a] 47.4%	12[a] 31.6%		4[a] 28.6%	231[a] 46.8%		186[a] 45.1%	49[a] 51.0%	
GDS6	GDS6- 247 48.6%	225[a] 47.9%	22[a] 57.9%	0.234	9[a] 64.3%	238[a] 48.2%	0.234	206[a] 50.0%	41[a] 42.7%	0.198
	GDS6+ 261 51.4%	245[a] 52.1%	16[a] 42.1%		5[a] 35.7%	256[a] 51.8%		206[a] 50.0%	55[a] 57.3%	
GDS5	GDS5- 327 64.4%	300[a] 63.8%	27[a] 71.1%	0.371	11[a] 78.6%	316[a] 64.0%	0.261	273[a] 66.3%	54[a] 56.3%	0.065
	GDS5+ 181 35.6%	170[a] 36.2%	11[a] 28.9%		3[a] 21.4%	178[a] 36.0%		139[a] 33.7%	42[a] 43.8%	
GDS4	GDS4- 264 52.0%	243[a] 51.7%	21[a] 55.3%	0.673	10[a] 71.4%	254[a] 51.4%	0.139	217[a] 52.7%	47[a] 49.0%	0.512
	GDS4+ 244 48.0%	227[a] 48.3%	17[a] 44.7%		4[a] 28.6%	240[a] 48.6%		195[a] 47.3%	49[a] 51.0%	
GDS4Lit	GDS4Lit- 43 8.5%	39[a] 8.3%	4[a] 10.5%	0.635	2[a] 14.3%	41[a] 8.3%	0.427	34[a] 8.3%	9[a] 9.4%	0.722
	GDS4Lit+ 465 91.5%	431[a] 91.7%	34[a] 89.5%		12[a] 85.7%	453[a] 91.7%		378[a] 91.7%	87[a] 90.6%	

Abbreviations: GDS: Geriatric Depression Scale; -: negative test; +: positive test; SD=Standard Deviation; GDS-Geriatric Depression State; GDS4Lit- 4 questions in questionnaire in the literature; GDS4-4 questions more frequent in pcb-Cohort; GDS5-5 more frequent questions in pcb-Cohort; GDS6-6 more frequent questions in pcb-Cohort; GDS7-7 more frequent questions in pcb-Cohort; GDS8-8 more frequent questions in pcb-Cohort; *APOE*-Apolipoprotein E. Number of allele carriers are indicatedε2/ε3/ε4. Data presented as N (%) and % is expressed % as a function of the total in each of the *APOE* allele. Statistical test used: χ2=Chi square test; Superscripts letters: [a.b] the same subscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value<0.05.

4.2.5.5 Multivariate analyses of the shorter GDS versions

In the light of all the results presented above, a bivariate evaluation of all the characteristics was carried out for all the GDS versions tested. The model was validated to determine the factors that contribute to a significant model to determine the parameters that behave as a risk factor; protective factor or not.

When determining the validity of the model, the optimal logistic model involved integration of: *APOE* carriers, sociodemographic characteristics, comorbidities and cognitive evaluation. This specific model was further analysed to evaluate statistical support for data integration in the evaluation of the best GDS short version. The Hosmer–Lemeshow statistic, the GDS15 had a p-value of 0.737; in the GDS8, a p-value of 0.699; in the GDS7, a p-value of 0.632; in the GDS6, p-value of 0.583; in the GDS5 p-value is 0.940; GDS4, p-value is 0.807 and to GDS4Lit, p-value is 0.780. The model fits the data, except for the GDS4Lit version, which features an Omnibus test of Model coefficients with $p>0.05$. All other versions have p-value<0.05.

Table 27 shows the multivariate analysis based on the Logistic regression enter methods to determine the possible risk factor(s) for depression with respect to the different GDS versions tested. Relative to GDS4Lit, it did not reveal a valid model, and furthermore no statistically significant correlation, at least for the pcb-Cohort.

Relative to GDS5, it is possible to see that *APOE ε4*, Female, CDR=0.5, IADL and depression history are important risk factors to determine possible depressive disorders. For the GDS6, the risk factors include: being female, scoring CDR=0.5, and a history of IADL and depression. For the GDS7, the risk factors are: being female, CDR=0.5, CDR≥1, literacy 3-6 years and depression history. For the GDS8, *APOE ε4* appears as a risk factor for depression, as well as being female, suspected cognitive impairment and a history of IADL and depression.

To GDS-15, the important factors with significance are: *APOE ε4*, being female, cognitive impairment based on the CDR, IADL, and a history of depression. These factors represent an increased risk, about twice as high, of having depression compared to individuals who do not have these characteristics.

Table 27 Multivariate analyses based on logistic regression for the shorter GDS versions

Characteristics	GDS-4Lit		GDS4		GDS5		GDS6		GDS7		GDS8		GDS-15	
	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR
ApoEe2	0.679	0.775	0.902	0.953	0.756	0.877	0.360	0.701	0.203	0.603	0.661	1.196	0.654	0.817
ApoEe3	0.610	1.608	**0.026**	4.523	**0.051**	4.201	0.059	3.388	0.094	3.076	0.055	3.736	0.530	1.517
ApoEe4	0.841	0.914	0.257	1.347	**0.026**	1.811	0.104	1.537	0.229	1.364	**0.001**	2.367	**0.051**	1.719
Gender	0.664	0.838	**0.009**	1.855	**0.003**	2.165	**0.002**	2.031	**0.024**	1.682	**0.013**	1.903	**0.005**	2.137
CDR=0.5	0.543	0.797	**0.001**	1.989	**0.002**	2.006	**0.027**	1.593	**0.017**	1.653	**0.001**	2.174	**<0.001**	2.615
CDR ≥ 1	0.946	0.961	0.063	1.942	0.081	1.871	0.094	1.836	**0.031**	2.158	0.153	1.675	**0.012**	2.526
MM	0.826	0.904	0.252	1.388	0.366	1.294	0.198	1.450	0.273	1.364	0.196	1.447	0.358	1.307
IADL	0.206	0.623	**0.006**	1.905	**0.001**	2.218	**0.005**	1.915	0.067	1.515	**0.009**	1.858	**<0.001**	2.340
Age Group[1]	0.679	1.105	0.166	0.822	0.980	0.996	0.355	0.879	0.855	0.975	0.697	.943	0.896	0.980
Literacy[2]	0.303	1.730	0.570	0.807	0.491	1.291	0.890	0.949	**0.048**	2.066	0.792	1.102	0.380	0.721
Literacy[3]	0.851	0.886	0.054	0.424	0.568	0.771	0.221	0.583	0.461	1.377	0.236	0.578	0.520	0.744
Depression[4]	0.846	0.933	**0.028**	1.602	**0.032**	1.597	**0.032**	1.585	**0.010**	1.726	**0.043**	1.563	**0.011**	1.772
Monthly income[5]	**0.048**	2.012	0.848	0.959	0.421	0.836	0.537	0.875	0.508	0.868	0.119	0.708	0.175	0.731

Abbreviations: GDS Geriatric Depression Scale; GDS-Geriatric Depression State; GDS4Lit- 4 questions in questionnaire in the literature; GDS4-4 questions more frequent in pcb-Cohort; GDS5-5 more frequent questions in pcb-Cohort; GDS6-6 more frequent questions in pcb-Cohort; GDS7-7 more frequent questions in pcb-Cohort; GDS8-8 more frequent questions in pcb-Cohort. CDR: Clinical Dementia Rate; OR: Odds Ratio; APOE Apolipoprotein E, allele ε2. ε3. ε4 carriers. Respectively; IADL: Instrumental Activities Daily Life; OR= risk or protective values in each parameters studied.[1] Age > 65 years old. [2] literacy 3-6 years . [3] literacy ≥ 7 years. Referent class in literacy is 0-2 years.[4] Depression History.[5] Monthly income more than 1 minimum wave.

4.2.6 Optimizing Criteria to Define Cases of Depression in the pcb-Cohort

Relative to depressive disorders, DSM-5 criteria for these pathologies was not applied. This is because the original questionnaire used was GDS, but this does not have all the items necessary to apply DSM-5 for depressive disorders. Because of this, depression was considered for individuals diagnosed with depression but also had to have confirmation in their respective clinical file from a psychiatric consultation.

This means that in this stage of the work, the patients excluded were:

1) Patients diagnosed in the clinical file without confirmation and

2) Patients with GDS15 positive without confirmation.

The results are explained in figure 10. Thus, for the subsequent studies in this section the cases of individuals with depression considered were 74 (herein referred to as TrueDEP/True depression cases).

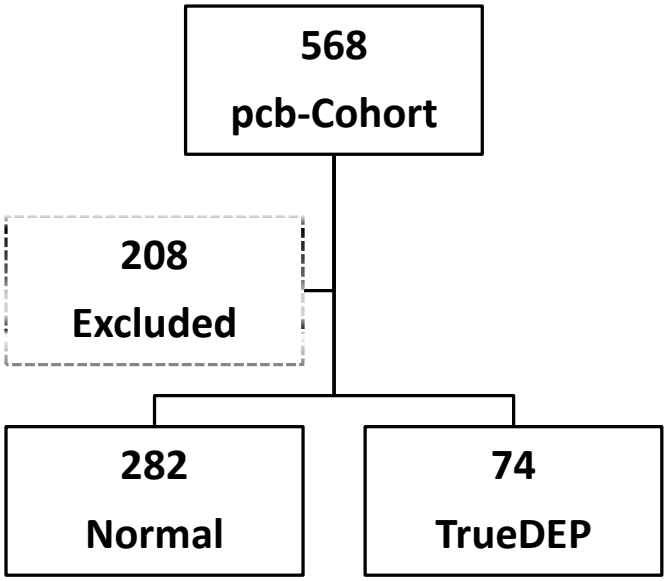


Figure 10 Workflow to identify cases of depression
A total of 208 patients were excluded because it was not possible to confirm the diagnostic of depression based on DSM-5. 286 patients did not have depression and the GDS is negative. 74 patients have a depression diagnostic confirmed by a specialist doctor and the GDS15 is positive.

4.2.7 Comparing the GDS15 and GDS4Lit for the True Depression Cases in the pcb-Cohort

Comparing the data here obtained with that of figure 8, it is immediately obvious that there is great consistency in the frequency and order of the top questions when considering each individual response of the GDS15. Again, for the TrueDEP the GDS4Lit does not perform well.

In detail, the top 8 most frequent depression positive questions are the same whether all the GDS15 positive cases (Figure 8) are considered or only the TrueDEP (Figure 11), with only one minor alteration; the order of question 5 and 7 (GDSQ5 and GDSQ7). That is the top 8 questions for GDS15 positive are (4, 6, 3, 9, 2, 5, 7 and 1) and for the TrueDEP (4, 6, 3, 9, 2, 7, 5 and 1). For the remaining 7 questions the overall order is consistent, although some minor alterations in the order of relative frequencies. Thus, for GDS15 the order is: 8, 14, 13, 15, 10, 12 and 11 and for the TrueDEP: 8, 13, 15, 10, 14, 12, and 11 (Figure 11).

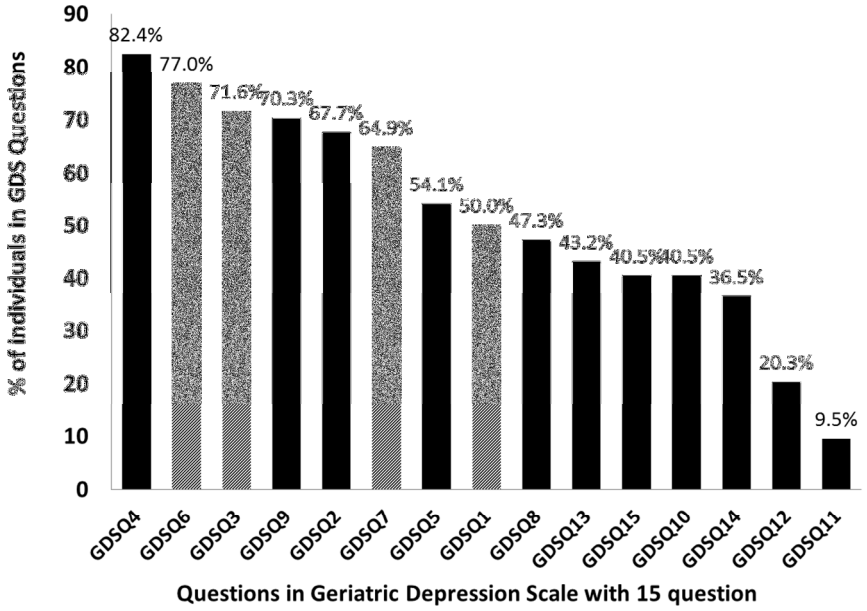


Figure 11- Frequency of answers consistent with depression in the GDS15 in patients with depression diagnostic in pcb-Cohort.

The number in front of GDS corresponds to the number of the question in the original GDS15 questionnaire (see methods); GDSQ4=question 4 in the GDS15. Stripped columns represent the four questions in the short version of GDS4Lit described in the literature. That is questions: GDSQ1. GDSQ3. GDSQ6 and GDSQ7 [186]. The percentage of individuals scoring in a pattern consistent with Depression, for each of the questions, is shown as a percentage of the total number of individuals with Depression (N=74).

4.2.8 Determining cut-off points for the Shorter GDS Versions Using the TrueDEP Cases

As above, the cut-off points for the shorter GDS versions were calculated but the TrueDEP cases were used as the reference for depression (Figure 12 and Table 28). Results are like those obtained when GDS15 is the reference for depression (Figure 9 and Table 20). The best cut offs for the different shorter GDS versions when TrueDEP cases are considered are: GDS8TrueDEP≥3; GDS7TrueDEP≥4; GDS6TrueDEP≥3; GDS5TrueDEP≥ 3; GDS4TrueDEP≥2. These are the same as those previously determined for the GDS15+, namely: GDS8≥3; GDS7≥4; GDS6≥3; GDS5≥3; GDS4≥2.

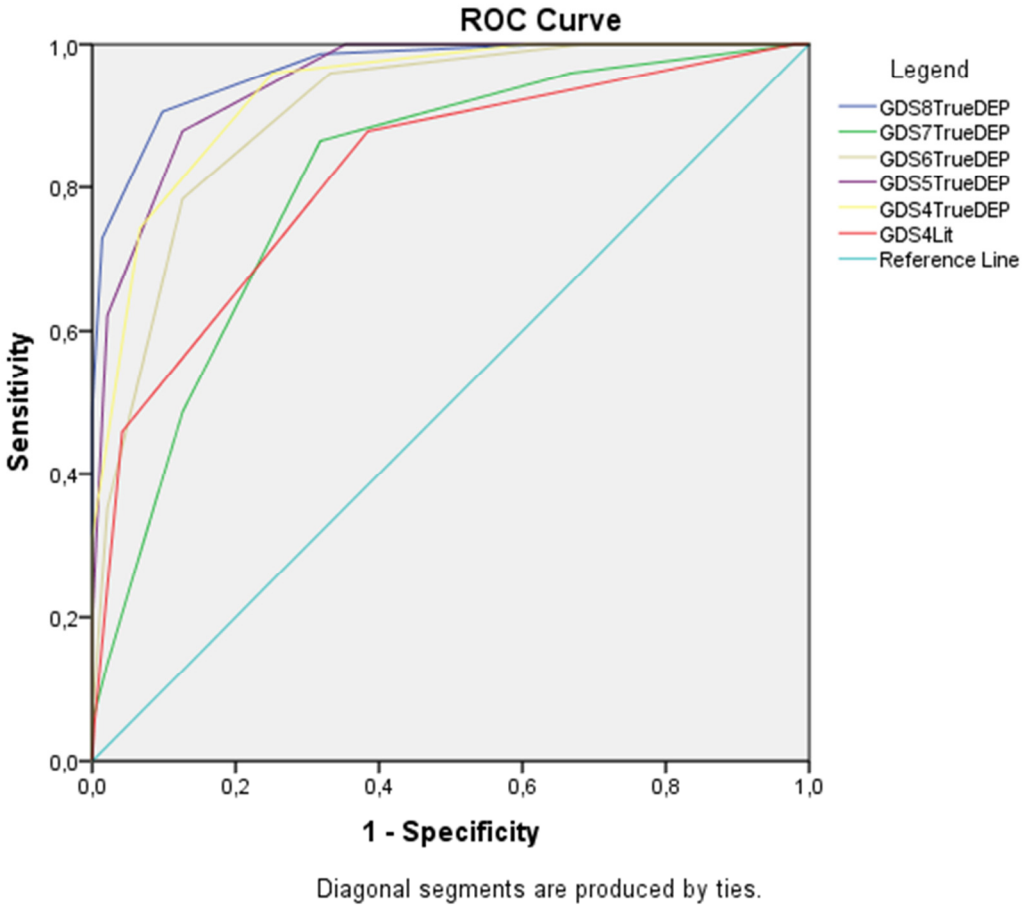


Figure 12 ROC Curve to GDS with short version based on TrueDEP cases

The number of questions in each of the GDS scales is as previously explained and based on the top incorrect answers of the GDS15. The AUC for GDS8 is 0.965 (CI 95% 0.945-0.985); for GDS7 it is 0.806 (95%CI 0.757-0.861); for GDS6 it is 0.904 (CI 95% 0.870 – 0.938); for GDS5 it is 0.947 (CI 95% 0.925-0.970); for GDS4 it is 0.934 (95%CI 0.906-0.961); and for GDS4Lit it is 0.812 (95%CI 0.762-0.874). The curves with the best discriminating power are GDS8 and GDS6. The null hypothesis: true area=0.5. Abbreviation: AUC=Area Under Curve; CI=Confidential Interval.

Table 28 ROC curve to determine cut-off points for the shorter GDS short versions based on TrueDEP

Test Result Variable(s)	Positive if Greater Than or Equal To	Sensitivity	Specificity
GDS8 TrueDEP	-1.0000	1.000	0.000
	0.5000	1.000	0.371
	1.5000	0.986	0.682
	2.5000	**0.905**	**0.902**
	3.5000	0.730	0.986
	4.5000	0.486	1.000
	5.5000	0.216	1.000
	6.5000	0.095	1.000
	7.5000	0.014	1.000
	9.0000	0.000	1.000
GDS7 TrueDEP	0.00	1.000	0.000
	1.50	1.000	0.014
	2.50	0.959	0.332
	3.50	**0.865**	**0.682**
	4.50	0.486	0.874
	5.50	0.135	0.979
	6.50	0.054	1.000
	8.00	0.000	1.000
GDS6 TrueDEP	-1.00	1.000	0.000
	0.50	1.000	0.003
	1.50	1.000	0.311
	2.50	**0.959**	**0.668**
	3.50	0.784	0.874
	4.50	0.351	0.979
	5.50	0.054	1.000
	7.00	0.000	1.000
GDS5 TrueDEP	-1.00	1.000	0.000
	0.50	1.000	0.311
	1.50	1.000	0.647
	2.50	0.878	0.874
	3.50	0.622	0.979
	4.50	0.189	1.000
	6.00	0.000	1.000
GDS4 TrueDEP	-1.00	1.000	0.000
	0.50	1.000	0.395
	1.50	**0.959**	**0.748**
	2.50	0.743	0.934
	3.50	0.311	1.000
	5.00	0.000	1.000
GDS4Lit	-1.00	1.000	0.000
	0.50	1.000	0.021
	1.50	**0.878**	**0.615**
	2.50	0.459	0.958
	3.50	0.054	0.997
	5.00	0.000	1.000

The test result variable(s): GDS8TrueDEP, GDS7TrueDEP, GDS6TrueDEP, GDS5TrueDEP, GDS4TrueDEP, GDS4Lit has at least one tie between the positive actual state group and the negative actual state group. The smallest cut-off value is the minimum observed test value minus 1. The largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

4.2.8.1 Determining the positive and negative predictive value of short versions by considering TrueDEP

The concept is as explained before, N=74 for patients with TrueDEP. Table 29 shows the correlation of the shorter GDS version and TrueDEP, as well as the sensibility (S), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV). To recall (Table 21), all proposed shorter GDS versions compared to GDS 15 present a statistically significant correlation with the latter, except for the version with four questions already described in the literature (GDS4Lit). Comparing to the TrueDEP based analysis (Table 29), results are similar except that GDS4Lit is also significant although the specificity level is very low (3.1).

To summarize all shorter GDS versions compared to TrueDEP exhibit similar statistical parameters (to distinguish from the above mentioned GDSn shorter versions, these are designated as GDSnTrueDEP). Thus, shorter GDS versions may be valuable tools, but of course this would have to be further validated.

Table 29 Predictive values to shorter GDS versions based on TrueDEP

Short Versions		N (%) 360	No Depression N=286	Depression N=74	p-value	S	SP	PPV	NPV
GDS8 TrueDEP	GDS8 TrueDEP -	265 (73.6%)	258[a] 90.2%	7[b] 9.5%	**<0.001**	90.5	90.2	69.4	97.4
	GDS8 TrueDEP +	95 (26.4%)	28[a] 9.8%	67[b] 90.5%					
GDS7 TrueDEP	GDS7 TrueDEP -	205 (56.9%)	195[a] 68.2%	10[b] 13.5%	**<0.001**	86.5	68.2	64.7	95.1
	GDS7 TrueDEP +	155 (43.1%)	91[a] 31.8%	64[b] 86.5%					
GDS6 TrueDEP	GDS6 TrueDEP -	194 (53.9%)	191[a] 66.8%	3[b] 4.1%	**<0.001**	95.9	66.8	71.7	98.5
	GDS6 TrueDEP +	166 (46.1%)	95[a] 33.2%	71[b] 95.9%					
GDS5 TrueDEP	GDS5 TrueDEP -	259 (71.9%)	250[a] 87.4%	9[b] 12.2%	**<0.001**	87.8	87.4	66.8	96.5
	GDS5 TrueDEP +	101 (28.1%)	36[a] 12.6%	65[b] 87.8%					
GDS4 TrueDEP	GDS4 TrueDEP -	217 (60.3%)	214[a] 74.8%	3[b] 4.1%	**<0.001**	95.9	74.8	72.0	98.6
	GDS4 TrueDEP +	143 (39.7%)	72[a] 25.2%	71[b] 95.9%					
GDS4Lit	GDS4Lit-	19 (5.3%)	9[a] 3.1%	10[b] 13.5%	**<0.001**	86.5	3.1	64.2	47.4
	GDS4Lit+	341 (94.7%)	277[a] 96.9%	64[b] 86.5%					

Abbreviation: GDS: Geriatric Depression Scale; -: negative test; +: positive test; GDS8TrueDEP is short version with eight questions pcb-Cohort; GDS7TrueDEP is short version with seven questions pcb-Cohort; GDS6TrueDEP is short version with six questions pcb-Cohort; GDS5TrueDEP is short version with five questions pcb-Cohort; GDS4TrueDEP is short version with four questions pcb-Cohort; GDS4Lit is short version with four questions in literature. S: Sensibility; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive value. PPV is the division of the true positives by the sum of patients. NPV-Negative predictive value is the division of true negatives by not ill. Statistical test: Statistical test used: $\chi 2$=Chi square test. Superscripts letters: [a.b]. The same superscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different superscript letters denote column proportions which differ significantly from each other at the 0.05 level. Tests are adjusted for all pairwise comparisons within a row of each innermost table using the Bonferroni correction.

4.2.8.2 Correlation of sociodemographic characteristics and shorter GDS versions based on TrueDEP

Sociodemographic characteristics in patients with shorter GDS versions based on TrueDEP (Table 30 and Table 31). For the TrueDEP group, there is a statistically significant correlation with all the parameters, except age: that is gender, marital status, living arrangement, professional status, monthly family income and level of education. These results are the same as when the GDS15+ was used as the control group (Tables 22 and 23).

Table 30 Sociodemographic characteristics and depression based on TrueDEP

Sociodemographic Characteristics	TrueDEP		p-value
	(-)	(+)	
Gender			
Male	113[a] (39.5%)	7[b] (9.5%)	**<0.001**
Female	173[a] (60.5%)	67[b] (90.5%)	
Age Group			
50-64	103[a] (36.0%)	28[a] (37.8%)	
65-74	112[a] (39.2%)	31[a] (41.9%)	0.714
≥ 75	71[a] (24.8%)	15[a] (20.3%)	
Marital Status			
Living with partner	218[a] (76.2%)	41[b] (55.4%)	**<0.001**
Others Situations	68[a] (23.8%)	33[b] (44.6%)	
Living Arrangement			
Alone	42[a] (14.7%)	20[b] (27.0%)	**0.012**
Accompanied	244[a] (85.3%)	54[b] (73.0%)	
Professional Status			
Active	84[a] (29.4%)	26[a] (35.1%)	
Reformed	192[a] (67.1%)	38[b] (51.4%)	**0.001**
Unemployed	10[a] (3.5%)	10[b] (13.5%)	
Monthly Family			
≤1MW	74[a] (25.9%)	31[b] (41.9%)	**0.007**
>1 MW	212[a] (74.1%)	43[b] (58.1%)	
Years of Literacy			
0-2 years of Literacy	18[a] (6.3%)	11[b] (14.9%)	
3-6 years of Literacy	203[a] (71.0%)	53[a] (71.6%)	**0.021**
>= 7 years of Literacy	65[a] (22.7%)	10[a] (13.5%)	

Abbreviation: GDS: TrueDEP- 74 patients with confirmed diagnostic to depressive disorder; (-) negative cases for depressive disorder; (+) the true positive cases for depressive disorder.

In Table 31, the shorter GDSnTrueDEP versions were compared to TrueDEP. To summarize the results were as follows, significant correlations with:

- GDS4Lit and monthly income;
- GDS4TrueDEP and monthly income, years of literacy and gender;
- GDS5TrueDEP and gender, living arrangement, monthly wage and years of literacy;
- GDS6TrueDEP and gender, monthly wage and years of literacy;
- GDS7TrueDEP and gender, marital status, living arrangement, monthly wage and years of literacy;
- GDS8TrueDEP and gender, marital status, living arrangement, monthly wage and years of literacy.

Therefore, GDS4Lit does not effectively characterize depression in the Portuguese pcb-Cohort. The short versions however do show similar results compared with TrueDEP, particularly so for GDS7TrueDEP and GDS8TrueDEP. These results are in line with those obtained with GDS15+ was employed for base line comparisons.

Table 31 Sociodemographic characteristics of shorter GDS versions based on TrueDEP

Sociodemographic Characteristics	GDS4Lit		*p*	GDS4TrueEDEP		*p*	GDS5TrueDEP		*p*	GDS6TrueDEP		*p*	GDS7TrueDEP		*p*	GDS8TrueDEP		*p*
	(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)	
Gender																		
Male	5 [a] (26%)	115 [a] (34%)	0.505	89 [a] (41%)	31 [b] (22%)	**<0.001**	101 [a] (39%)	19 [b] (19%)	**<0.001**	81 [a] (41.8%)	39 [b] (23.5%)	**<0.001**	83 [a] (40.5%)	37 [b] (23.9%)	**<0.001**	107 [a] (40.4%)	13 [b] (13.7%)	**<0.001**
Female	14 [a] (74%)	226 [a] (66%)		128 [a] (59%)	112 [b] (78%)		158 [a] (61%)	82 [b] (81%)		113 [a] (58.2%)	127 [b] (76.5%)		122 [a] (59.5%)	118 [b] (76.1%)		158 [a] (59.6%)	82 [b] (86.3%)	
Age Group																		
50-64	7 [a] (37%)	124 [a] (36%)	0.655	81 [a] (37%)	50 [a] (35%)	0.230	99 [a] (38%)	32 [a] (32%)	0.252	75 [a] (38.7%)	56 [a] (33.7%)	0.937	82 [a] (40.0%)	49 [a] (31.6%)	0.151	98 [a] (37.0%)	33 [a] (34.7%)	0.385
65-74	9 [a] (47%)	134 [a] (39%)		79 [a] (36%)	64 [a] (45%)		96 [a] (37%)	47 [a] (47%)		70 [a] (36.1%)	73 [a] (44.0%)		73 [a] (35.6%)	70 [a] (45.2%)		100 [a] (37.7%)	43 [a] (45.3%)	
≥ 75	3 [a] (16%)	83 [a] (24%)		57 [a] (26%)	29 [a] (20%)		64 [a] (25%)	22 [a] (22%)		49 [a] (25.3%)	37 [a] (22.3%)		50 [a] (24.4%)	36 [a] (23.2%)		67 [a] (25.3%)	19 [a] (20.0%)	
Marital Status																		
Living with partner	14 [a] (74%)	245 [a] (72%)	0.862	163 [a] (75%)	96 [a] (67%)	0.099	193 [a] (75%)	66 [a] (65%)	0.082	147 [a] (75.8%)	112 [a] (67.5%)	0.080	156 [a] (76.1%)	103 [b] (66.5%)	**0.044**	202 [a] (76.2%)	57 [b] (60.0%)	**0.003**
Others Situations	5 [a] (26%)	96 [a] (28%)		54 [a] (25%)	47 [a] (33%)		66 [a] (25%)	35 [a] (35%)		47 [a] (24.2%)	54 [a] (32.5%)		49 [a] (23.9%)	52 [b] (33.5%)		63 [a] 23.8%)	38 [b] (40.0%)	
Living Arrangement																		
Alone	4 [a] (21%)	58 [a] (17%)	0.650	31 [a] (14%)	31 [a] (22%)	0.069	38 [a] (15%)	24 [b](24%)	**0.040**	27 [a] (13.9%)	35 [a] (21.1%)	0.073	28 [a] (13.7%)	34 [b] (21.9%)	**0.039**	38 [a] (14.3%)	24 [b] (25.3%)	**0.016**
Accompanied	15 [a] (79%)	283 [a] (83%)		186 [a] (86%)	112 [a] (78%)		221 [a] (85%)	77 [b] (76%)		167 [a] (86.1%)	131 [a] (78.9%)		177 [a] (86.3%)	121 [b] (78.1%)		227 [a] (85.7%)	71 [b] (74.7%)	
Professional Status																		
Active	9 [a] (47%)	101 [a] (30%)	0.257	70 [a] (32%)	40 [a] (28%)	0.138	84 [a] (32%)	26 [a] (26%)	0.138	64 [a] (33.0%)	46 [a] (27.7%)	0.157	69 [a] (33.7%)	41 [a] (26.5%)	0.312	81 [a] (30.6%)	29 [a] (30.5%)	0.144
Reformed	9 [a] (47%)	221 [a] (65%)		139 [a] (64%)	91 [a] (64%)		164 [a] (63%)	66 [a] (65%)		123 [a] (63.4%)	107 [a] (64.5%)		126 [a] (61.5%)	104 [a] (67.1%)		173 [a] (65.3%)	57 [a] (60.0%)	
Unemployed	1 [a] (5%)	19 [a] (6%)		8 [a] (4%)	12 [a] (8%)		11 [a] (4%)	9 [a] (9%)		7 [a] (3.6%)	13 [a] (7.8%)		10 [a] (4.9%)	10 [a] (6.5%)		11 [a] (4.2%)	9 [a] (9.5%)	
Monthly Family																		
≤1MW	10 [a] (53%)	95 [b] (28%)	**0.021**	53 [a] (24%)	52 [b] (36%)	0.015	68 [a] (26%)	37 [a] (37%)	**0.052**	46 [a] (23.7%)	59 [b] (35.5%)	**0.014**	50 [a] (24.4%)	55 [b] (35.5%)	**0.022**	69 [a] (26.0%)	36 [b] (37.9%)	**0.029**
>1 MW	9 [a] (47%)	246 [b] (72%)		164 [a] (76%)	91 [b] (64%)		191 [a] (74%)	64 [a] (63%)		148 [a] (76.3%)	107 [b] (64.5%)		155 [a] (75.6%)	100 [b] (64.5%)		196 [a] (74.0%)	59 [b] (62.1%)	
Years of Literacy																		
0-2 years of Literacy	1 [a] (5%)	28 [a] (8%)	0.427	11 [a] (5%)	18 [b] (13%)	**<0.000**	16 [a] (6%)	13 [b](13%)	**0.004**	9 [a] (4.6%)	20 [b] (12.0%)	**<0.001**	13 [a] (6.3%)	16 [a] (10.3%)	**0.016**	17 [a] (6.4%)	12 [a] (12.6%)	**0.011**
3-6 years of Literacy	16 [a] (84%)	240 [a] (70%)		145 [a] (67%)	111 [b] (78%)		179 [a] (69%)	77 [a] (76%)		132 [a] (68.0%)	124 [a] (74.7%)		139 [a] (67.8%)	117 [a] (75.5%)		184 [a] (69.4%)	72 [a] (75.8%)	
>= 7 years of Literacy	2 [a] (11%)	73 [a] (21%)		61 [a] (28%)	14 [b] (10%)		64 [a] (25%)	11 [b] (11%)		53 [a] (27.3%)	22 [b] (13.3%)		53 [a] (25.9%)	22 [b] (14.2%)		64 [a] (24.2%)	11 [b] (11.6%)	

Abbreviations: GDSnTrueDEP-short version with "n" questions based in 74 patients with confirmed diagnosis of depression in pcb-Cohort. Abbreviation: GDS: TrueDEP- 74 patients with confirmed diagnostic to depressive disorder; (-) negative cases for depressive disorder; (+) the true positive cases for depressive disorder.

4.2.8.3 Correlation of shorter GDS versions based on TrueDEP and comorbidities

Table 32 shows the correlation of clinical characteristics and TrueDEP cases of depressive disorder. The comorbidities that show correlation are OA and GID, both with statistical significance. As explained before, N=356 patients from the pcb-Cohort (286 negative cases and 74 positive cases).

Table 32 Correlation comorbidities with TrueDEP

Comorbidities	N (%) 356	TrueDEP				p-value
		(-) N=286		(+) N=74		
HTA	223 (61.9%)	176[a]	(61.5%)	47[a]	(63.5%)	0.755
DYS	214 (59.4%)	168[a]	(58.7%)	46[a]	(62.2%)	0.593
OA	188 (52.2%)	136[a]	(47.6%)	52[b]	(70.3%)	**<0.001***
CVD	196 (54.4%)	156[a]	(54.5%)	40[a]	(54.1%)	0.940
GID	90 (25.0%)	56[a]	(19.6%)	34[b]	(45.9%)	**<0.001***
GUD	76 (21.1%)	60[a]	(21.0%)	16[a]	(21.6%)	0.904
DM	75 (20.8%)	61[a]	(21.3%)	14[a]	(18.9%)	0.649
RESP	60 (16.7%)	45[a]	(15.7%)	15[a]	(20.3%)	0.351
HEMATO	42 (11.7%)	33[a]	(11.5%)	9[a]	(12.2%)	0.882
NEURO	10 (2.8%)	7[a]	(2.4%)	3[a]	(4.1%)	0.4541
ALCOHOL	10 (2.8%)	9[a]	(3.1%)	1[a]	(1.4%)	0.4021

Abbreviations: TrueDEP-74 patients with confirmed diagnostic to depressive disorder; (-) negative cases for depressive disorder; (+) the true positive cases for depressive disorder. HYP-Hypertension arterial; DYS-Dyslipidaemia; OA-Osteoarthicular disease; CVD-Cardiac and vascular Disease; DEP-Depression; GID-Gastrointestinal Disease; GUD-Genitourinary Disease; DM-Diabetes Mellitus; RESP-Respiratory Disease; HEMATO-Hematologic Disease; ONCO-Oncology Disease; NEURO-Neuropathologies; ALCOHOL-Alcohol Excessive Use. Statistical test: *χ2-Chi square test. Values in the same row and not sharing the same superscript are significantly different at *p<0.05* in the two-sided test of equality for column proportions. N=356 patients of pcb-Cohort. Superscripts letters [a, b]: The same subscript letter denotes a subset of categories whose column proportions don not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level. In bold, the p-value less than 0.05. Tests assume equal variances. Tests are adjusted for all pairwise comparisons within a row of each innermost using the Bonferroni correction.

In Table 33 the correlations of the shorter version based on TrueDEP cases with comorbidities are shown. For GDS4Lit, there are not correlations, but for all the other

cases the correlations with OA and GID are confirmed, with statistical significance. This is consistent with the results seen when GDS15+ cases were taken as the depressed participants (Table 24).

Table 33 Correlation of comorbidities with shorter GDS versions based on TrueDEP

Comorbidities	N	GDS4Lit		*p*	GDS4TrueDEP		*p*	GDS5TrueDEP		*p*	GDS6TrueDEP		*p*	GDS7TrueDEP		*p*	GDS8TrueDEP		*p*
		(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)		(-)	(+)	
HTA	223 (61,9%)	12^{a} (63.2%)	211^{a} (61.9%)	0.911	124^{a} (57.1%)	99^{b} (69.2%)	**0.021**	153^{a} (59.1%)	70^{a} (69.3%)	0.072	113^{a} (58.2%)	110^{a} 66.3%)	0.118	120^{a} (58.5%)	103^{a} (66.5%)	0.126	161^{a} (60.8%)	62^{a} (65.3%)	0.437
DYS	214 (59,4%)	12^{a} (63.2%)	202^{a} 59.2%)	0.735	125^{a} (57.6%)	89^{a} (62.2%)	0.381	150^{a} (57.9%)	64^{a} (63.4%)	0.344	108^{a} (55.7%)	106^{a} (63.9%)	0.115	114^{a} (55.6%)	100^{a} (64.5%)	0.088	155^{a} (58.5%)	59^{a} (62.1%)	0.538
OA	188 (52,2%)	14^{a} (73.7%)	174^{a} (51.0%)	0.054	98^{a} (45.2%)	90^{b} (62.9%)	**<0.001**	118^{a} (45.6%)	70^{b} (69.3%)	**<0.001**	85^{a} (43.8%)	103^{b} (62.0%)	**0.001**	93^{a} (45.4%)	95^{b} (61.3%)	**0.003**	122^{a} (46.0%)	66^{b} (69.5%)	**<0.001**
CVD	196 (54,4%)	10^{a} (52.6%)	186^{a} (54.5%)	0.870	116^{a} (53.5%)	80^{a} (55.9%)	0.643	136^{a} (52.5%)	60^{a} (59.4%)	0.238	102^{a} (52.6%)	94^{a} (56.6%)	0.442	108^{a} (52.7%)	88^{a} (56.8%)	0.440	144^{a} (54.3%)	52^{a} (54.7%)	0.947
GID	90 (25,0%)	8^{a} (42.1%)	82^{a} (24.0%)	0.077	38^{a} (17.5%)	52^{b} (36.4%)	**<0.001**	46^{a} (17.8%)	44^{b} (43.6%)	**<0.001**	36^{a} (18.6%)	54^{b} (32.5%)	**0.002**	40^{a} (19.5%)	50^{b} (32.3%)	**0.006**	48^{a} (18.1%)	42^{b} (44.2%)	**<0.001**
GUD	76 (21,1%)	6^{a} (31.6%)	70^{a} (20.5%)	0.251	46^{a} (21.2%)	30^{a} (21.0%)	0.960	51^{a} (19.7%)	25^{a} (24.8%)	0.290	40^{a} (20.6%)	36^{a} (21.7%)	0.804	41^{a} (20.0%)	35^{a} (22.6%)	0.552	55^{a} (20.8%)	21^{a} (22.1%)	0.782
DM	75 (20,8%)	5^{a} (26.3%)	70^{a} (20.5%)	0.545	47^{a} (21.7%)	28^{a} (19.6%)	0.635	55^{a} (21.2%)	20^{a} (19.8%)	0.763	44^{a} (22.7%)	31^{a} (18.7%)	0.351	48^{a} (23.4%)	27^{a} (17.4%)	0.165	56^{a} (21.1%)	19^{a} (20.0%)	0.816
RESP	60 (16,7%)	6^{a} (31.6%)	54^{a} (15.8%)	0.073	31^{a} (14.3%)	29^{a} (20.3%)	0.135	41^{a} (15.8%)	19^{a} (18.8%)	0.495	27^{a} (13.9%)	33^{a} (19.9%)	0.130	28^{a} (13.7%)	32^{a} (20.6%)	0.078	42^{a} (15.8%)	18^{a} (18.9%)	0.487
HEMATO	42 (11,7%)	2^{a} (10.5%)	40^{a} (11.7%)	0.874	20^{a} (9.2%)	22^{a} (15.4%)	0.074	28^{a} (10.8%)	14^{a} (13.9%)	0.418	19^{a} (9.8%)	23^{a} (13.9%)	0.231	20^{a} (9.8%)	22^{a} (14.2%)	0.194	28^{a} (10.6%)	14^{a} (14.7%)	0.277
NEURO	10 (2,8%)	0^{a} (0.0%)	10^{a} (2.9%)	0.449	5^{a} (2.3%)	5^{a} (3.5%)	0.501^{b}	7^{a} (2.7%)	3^{a} (3.0%)	0.890	3^{a} (1.5%)	7^{a} (4.2%)	0.124	3^{a} (1.5%)	7^{a} (4.5%)	0.081	6^{a} (2.3%)	4^{a} (4.2%)	0.322^{b}
ALCOHOL	10 (2,8%)	0^{a} (0.0%)	10^{a} (2.9%)	0.449	7^{a} (3.2%)	3^{a} (2.1%)	0.524	9^{a} (3.5%)	1^{a} (1.0%)	0.197	7^{a} (3.6%)	3^{a} (1.8%)	0.300	8^{a} (3.9%)	2^{a} (1.3%)	0.135	8^{a} (3.0%)	2^{a} (2.1%)	0.642^{b}

Abbreviations: GDS-Geriatric Depression Scale; GDSnTrueDEP-short version with "n" questions based in 74 patients with confirmed diagnosis of depression in pcb-Cohort; -: negative test; +: positive test. HYP: Hypertension; DYL: Dyslipidemia; CVD: Cardiac and vascular disease; GID: Gastrointestinal Disease; GUD: Genitourinary disease; DM: Diabetes Mellitus; RESP: Respiratory Disease; HEMATO: Hematology Disease; NEURO: Neuropathology. Statistical test used: χ2=Chi square test. Superscripts letters: ^{a,b}. The same superscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different superscript letters denote column proportions which differ significantly from each other at the 0.05 level. Tests are adjusted for all pairwise comparisons within a row of each innermost table using the Bonferroni correction. In bold, p-value<0.05.

4.2.8.4 Correlation of TrueDEP shorter GDS versions and cognitive evaluation with CDR and MMSE

True depression cases (TrueDEP) were correlated with CDR and MMSE scores. In both cases no correlations occurred with GDS4Lit. Regarding all the other cases GDSnTrueDEP correlations are significant in all cases except for MMSE and GDS7TrueDEP (Table 34). The results are like those shown in the GDS15 correlations (Table 21). Taken together one can deduce that there is a strong correlation with cognitive impairment and depression.

Table 34 Correlation of depressive disorders and TrueDEP shorter GDS versions

GDS version	N (%)	CDR			p-value	MMSE		p-value
		CDR=0 N=301	CDR=0.5 N=199	CDR≥1 N=68		MMSE- N=436	MMSE+ N=132	
TrueDEP	Dep- N=282	189[a] 89.6%	76[b] 67.3%	21[b] 58.3%	**<0.001**	270[a] 82.1%	16[b] 51.6%	**<0.001**
	Dep+ N=74	22[a] 10.4%	37[b] 32.7%	15[b] 41.7%		59[a] 17.9%	15[b] 48.4%	
GDS8 TrueDEP	GDS8PCB- N=265	171[a] 81.0%	73[b] 64.6%	21[b] 58.3%	**<0.001**	247[a] 75.1%	18[b] 58.1%	**0.040**
	GDS8PCB+ N=95	40[a] 19.0%	40[b] 35.4%	15[b] 41.7%		82[a] 24.9%	13[b] 41.9%	
GDS7 TrueDEP	GDS7PCB- N=205	137[a] 64.9%	56[b] 49.6%	12[b] 33.3%	**<0.001**	192[a] 58.4%	13[a] 41.9%	0.077
	GDS7PCB+ N=155	74[a] 35.1%	57[b] 50.4%	24[b] 66.7%		137[a] 41.6%	18[a] 58.1%	
GDS6 TrueDEP	GDS6PCB- N=194	131[a] 62.1%	52[b] 46.0%	11[b] 30.6%	**<0.001**	183[a] 55.6%	11[b] 35.5%	**0.032**
	GDS6PCB+ N=166	80[a] 37.9%	61[b] 54.0%	25[b] 69.4%		146[a] 44.4%	20[b] 64.5%	
GDS5 TrueDEP	GDS5PCB- N=259	171[a] 81.0%	68[b] 60.2%	20[b] 55.6%	**<0.001**	243[a] 73.9%	16[b] 51.6%	**0.008**
	GDS5PCB+ N=101	40[a] 19.0%	45[b] 39.8%	16[b] 44.4%		86[a] 26.1%	15[b] 48.4%	
GDS4 TrueDEP	GDS4PCB- N=217	148[a] 70.1%	55[b] 48.7%	14[b] 38.9%	**<0.001**	204[a] 62.0%	13[b] 41.9%	**0.029**
	GDS4PCB+ N=143	63[a] 29.9%	58[b] 51.3%	22[b] 61.1%		125[a] 38.0%	18[b] 58.1%	
GDS4Lit	GDS4Lit- N=19	8[a] 3.8%	10[a] 8.8%	1[a] 2.8%	0.118	17[a] 5.2%	2[a] 6.5%	0.760
	GDS4Lit+ N=341	203[a] 96.2%	103[a] 91.2%	35[a] 97.2%		312[a] 94.8%	29[a] 93.5%	

Abbreviation: GDS: Geriatric Depression Scale; GDSnTrueDEP-short version with "n" questions based in 74 patients with confirmed diagnosis of depression in pcb-Cohort; -: negative test; +: positive test. -: negative test; +: positive test; GDS4Lit is short version with four questions in literature. CDR-Clinical Dementia Rate; MMSE-Mini Mental Status Examination. Superscripts letters: [a.b]. The same superscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different superscript letters denote column proportions which differ significantly from each other at the 0.05 level. Tests are adjusted for all pairwise comparisons within a row of each innermost table using the Bonferroni correction.

4.2.8.5 *Correlation of TrueDEP shorter GDS versions and APOE* genotyping

APOE and depression have previously been correlated in literature [200]. Subsequently the different TrueDEP shorter versions were compared to the *APOE* genotype (Table 35). There are no correlations with statistical significance, in any of the shorter version based on TrueDEP cases. This is strikingly different to the results obtained in the GDS15, when in fact APOEe4 correlated with a depressive condition as determined by GDS15+ and GDS8+ (Table 26).

Table 35 Correlation of depressive disorders based on TrueDEP shorter GDS versions and *APOE* genotyping

		APOE								
GDS Versions	**N (%)**	**Non ε2 carriers N=303**	**ε2 carriers N=23**	**p-value**	**Non ε3 carriers N=4**	**ε3 carriers N=322**	**p-value**	**Non ε4 carriers N=271**	**ε4 carriers N=55**	**p-value**
TrueDEP	GDS15- N=259	240[a] 79.2%	19[a] 82.6%	0.697	3[a] 75.0%	256[a] 79.5%	0.825	217[a] 80.1%	42[a] 76.4%	0.535
	GDS15+ N=67	63[a] 20.8%	4[a] 17.4%		1[a] 25.0%	66[a] 20.5%		54[a] 19.9%	13[a] 23.6%	
GDS8 TrueDEP	GDS8- N=241	224[a] 73.9%	17[a] 73.9%	0.999	3[a] 75.0%	238[a] 73.9%	0.961	205[a] 75.6%	36[a] 65.5%	0.117
	GDS8+ N=85	79[a] 26.1%	6[a] 26.1%		1[a] 25.0%	84[a] 26.1%		66[a] 24.4%	19[a] 34.5%	
GDS7 TrueDEP	GDS7- N=190	174[a] 57.4%	16[a] 69.6%	0.255	2[a] 50.0%	188[a] 58.4%	0.735	163[a] 60.1%	27[a] 49.1%	0.129
	GDS7+ N=136	129[a] 42.6%	7[a] 30.4%		2[a] 50.0%	134[a] 41.6%		108[a] 39.9%	28[a] 50.9%	
GDS6 TrueDEP	GDS6- 179	164[a] 54.1%	15[a] 65.2%	0.303	2[a] 50.0%	177[a] 55.0%	0.843	154[a] 56.8%	25[a] 45.5%	0.122
	GDS6+ 147	139[a] 45.9%	8[a] 34.8%		2[a] 50.0%	145[a] 45.0%		117[a] 43.2%	30[a] 54.5%	
GDS5 TrueDEP	GDS5- N=234	215[a] 71.0%	19[a] 82.6%	0.231	3[a] 75.0%	231[a] 71.7%	0.885	198[a] 73.1%	36[a] 65.5%	0.253
	GDS5+ N=92	88[a] 29.0%	4[a] 17.4%		1[a] 25.0%	91[a] 28.3%		73[a] 26.9%	19[a] 34.5%	
GDS4 TrueDEP	GDS4- N=197	182[a] 60.1%	15[a] 65.2%	0.626	3[a] 75.0%	194[a] 60.2%	0.549	165[a] 60.9%	32[a] 58.2%	0.709
	GDS4+ N=129	121[a] 39.9%	8[a] 34.8%		1[a] 25.0%	128[a] 39.8%		106[a] 39.1%	23[a] 41.8%	
GDS4Lit	GDS4Lit- N=19	16[a] 5.3%	3[a] 13.0%	0.126	0[1] 0.0%	19[a] 5.9%	0.617	15[a] 5.5%	4[a] 7.3%	0.616
	GDS4Lit+ N=307	287[a] 94.7%	20[a] 87.0%		4[1] 100.0%	303[a] 94.1%		256[a] 94.5%	51[a] 92.7%	

Abbreviation: GDS: Geriatric Depression Scale; GDSnTrueDEP-short version with "n" questions based in 74 patients with confirmed diagnosis of depression in pcb-Cohort; -: negative test; +: positive test. -; APOE-Apolipoprotein E. Number of allele carriers are indicatedε2/ε3/ε4. Data presented as N (%) and % is expressed % as a function of the total in each of the APOE allele. Superscripts letters: a.b. The same superscript letter denotes a subset of GDS categories whose column proportions do not differ significantly from each other at the 0.05 level. Different superscript letters denote column proportions which differ significantly from each other at the 0.05 level. Tests are adjusted for all pairwise comparisons within a row of each innermost table using the Bonferroni correction.

4.2.8.6 Logistic Regression to determine risk factors for depressive status based on GDSnTrueDEP

In the light of all these results, a bivariate evaluation of all the characteristics was carried out for depressive cases and for all the GDSnTrueDEP scales tested. The model was validated. To determine the factors that are important to a significant model and of these factors, which behave as a risk factor, protective factor, or as a factor not bearing a statistically significant contribution, through the odds ratio. The optimal logistic model involved integration of: *APOE* carriers, sociodemographic characteristics, comorbidities and cognitive evaluation. This specific model was further analysed to evaluate statistical support for data integration in the evaluation of the best GDS short version. The Hosmer–Lemeshow statistic, in the depressive disorder cases, had a p-value of 0.401; in the GDS8TrueDEP, a p-value of 0.184; in the GDS7TrueDEP, a p-value of 0.385; in the GDS6TrueDEP, p-value of 0.358; in the GDS5TrueDEP, p-value is 0.421; in GDS4 TrueDEP, p-value is 0.139 and to GDS4Lit, p-value is 0.338. The model fits the data, except for the GDS4Lit version, which features an Omnibus test of Model coefficients with $p>0.05$. All other versions have p-value<0.05. The Logistic Regression was performed to find important risk factors in different GDSnTrueDEP versions. Table 36 shows all OR and p-values.

Significant correlations were seen with gender, cognitive impairment based on the CDR, IADL, and age. These factors represent an increased risk, about twice as high, with respect to having depression (Table 36). The shorter versions GDSnTrueDEP behave in a similar fashion but with GDS4Lit there are no significant correlations.

Table 36 Multivariate analysis based on logistic regression TrueDEP shorter GDS versions

Characteristics	GDS-4Lit		GDS4TrueDEP		GDS5TrueDEP		GDS6TrueDEP		GDS7TrueDEP		GDS8TrueDEP		TrueDEP	
	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR	SIG	OR
APOEε2	0.052	0.223	0.537	0.730	0.237	0.478	0.267	0.569	0.365	0.627	0.918	1.058	0.655	0.750
APOEε3	0.999	0.000	0.361	3.190	0.658	1.827	0.811	1.315	0.855	1.234	0.561	2.144	0.875	0.801
APOEε4	0.253	0.488	0.912	1.038	0.372	1.367	0.261	1.450	0.304	1.399	0.163	1.639	0.892	1.058
Female	0.969	0.977	**0.001**	2.799	**<0.001**	3.452	**<0.001**	2.761	**<0.001**	2.580	**<0.001**	5.218	**<0.001**	9.697
CDR=0.5	0.239	0.522	0.056	1.692	**0.049**	1.791	0.262	1.355	0.160	1.460	0.223	1.451	**0.010**	2.480
CDR ≥ 1	0.475	2.595	0.022	3.294	0.271	1.782	**0.044**	2.840	**0.013**	3.610	0.100	2.421	**0.013**	4.340
MM	0.491	0.486	0.485	0.674	0.790	1.163	0.464	0.661	0.236	0.514	0.323	0.556	0.940	1.047
IADL	0.145	0.440	**0.019**	2.039	**0.004**	2.470	**0.005**	2.329	**0.015**	2.050	**0.015**	2.235	**0.002**	3.034
Age Group[1]	0.808	0.871	0.675	0.885	0.552	1.205	0.976	1.009	0.484	1.219	0.868	0.948	0.175	0.610
Age Group[2]	0.418	1.890	0.060	0.505	0.363	0.699	0.262	0.677	0.792	0.913	0.348	0.686	0.054	0.404
Lliteracy[3]	0.233	0.262	0.547	0.762	0.867	0.925	0.329	0.634	0.874	1.073	0.832	0.906	0.919	1.053
Literacy[4]	0.430	0.343	**0.019**	0.268	0.161	0.435	**0.025**	0.291	0.338	0.599	0.215	0.475	0.750	0.809
Monthly Family Income	**0.020**	3.495	0.913	0.970	0.836	0.940	0.982	1.006	0.965	0.988	0.880	0.955	0.368	0.739

Abbreviations: GDS Geriatric Depression Scale; GDSnTrueDEP-short version with "n" questions based in 74 patients with confirmed diagnosis of depression in pcb-Cohort; CDR: Clinical Dementia Rate; OR: Odds Ratio; *APOE*: Apolipoprotein E. allele ε2, ε3, ε4 carriers, respectively; IADL: Instrumental Activities Daily Life; OR=risk or protective values in each parameters studied. Superscript numbers: [1] Age 65-74 years old; [2] Age Group ≥75 years old; [3]literacy 3-6 years; [4] literacy ≥ 7 years. Referent class: in Age Group. It is 50-64 years old; in literacy. It is 0-2 years. Relative to Monthly income, the value is more than 1 minimum wave. In bold, the value of p-value<0.05.

Results
4.3 APOE Genotyping of the pcb-Cohort

4.3.1 *APOE* Genotype Frequency in the pcb-Cohort

Several genetic risk factors have been associated with AD, but as mentioned in the introduction *APOE* is the best studied risk factor. Specifically, the presence of the *APOE* alleleε4 is a known risk factor for AD. Thus, the pcb-Cohort was genotyped for *APOE* (Figure 13). The most prevalent *APOE* genotype is theε3ε3, expressed in 75% of the individuals,ε3ε4 in 16.1% andε2ε3 in 6.1%. Noε2ε2 individuals are evident and lower percentages of 1.4% can be seen for bothε2ε4 andε4ε4.

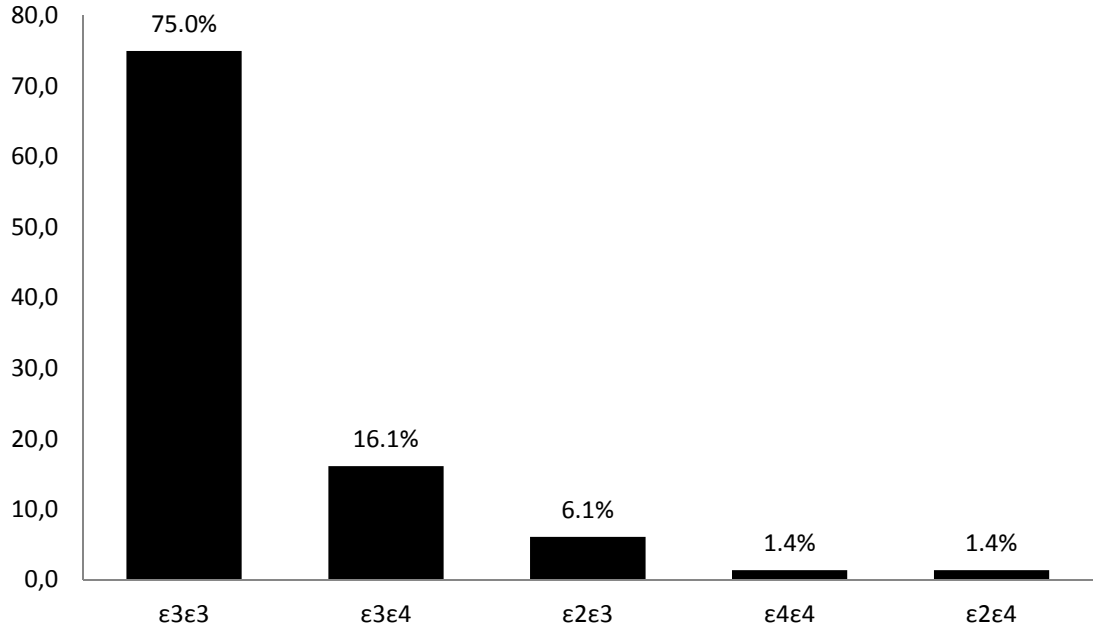


Figure 13 *APOE* genotype in the pcb-Cohort
The more frequent genotype isε3ε3. There are noε2ε2. The prevalence ofε2ε4 andε4ε4 is 1.4%.

4.3.2 *APOE* Polymorphisms Correlations with Ageing and Cognitive Decline

Relevant characteristics, namely socio-demographic and cognitive decline within the pcb-Cohort and corresponding associations with *APOE ε4*,ε3 andε2 carriers were carried out. No significant associations are evident for alleleε3 carriers (data not shown), with respect to *APOE ε4* andε2 alleles (Table 35). No statistically significant gender related associations were found. However, for the younger age group in the pcb-Cohort population (age group from 50-64 years old) there is a significant correlation with the *APOE ε2* carriers (p=0.042).

Table 37 Sociodemographic and cognitive characteristics in *APOEε4* and *APOEε2* carriers

Socio-demographic Characteristics	N=508	*APOE* ε4- N=412	*APOE* ε4+ N=96	p-value	*APOE* ε2- N=470	*APOE* ε2+ N=38	p-value
Gender*							
Male	152 (29.9%)	119 [a] (28.9%)	33 [a] (34.4%)	0.290	144 [a] (30.6%)	8 [a] (21.1%)	0.215
Female	356 (70.1%)	293 [a] (71.1%)	63 [a] (65.6%)		326 [a] (69.4%)	30 (78.9%)	
Age Group*							
[50-64] years	177 (34.8%)	145 [a] (35.2%)	32 [a] (33.3%)	0.926	157 [a] (33.4%)	20 [b] (52.6%)	**0.042**
[65-74] years	205 (40.4%)	166 [a] (40.3%)	39 [a] (40.6%)		192 [a] (40.9%)	13 [b] (34.2%)	
[≥75] years	126 (24.8%)	101 [a] (24.5%)	25 [a] (26.0%)		121 [a] (25.7%)	5 [b] (13.2%)	
Cognitive Characteristics	**N (%)**	***APOE* ε4- N=412**	***APOE* ε4+ N=96**	**p-value**	***APOE* ε2- N=470**	***APOE* ε2+ N=38**	**p-value**
CDR*							
CDR=0	256 (50.4%)	216 [a] (52.4%)	40 [a] (41.7%)	**0.035**	233 [a] (49.6%)	23 [a] (60.5%)	0.390
CDR=0.5	188 (37.0%)	151 [a] (36.7%)	37 [a] (38.5%)		176 [a] (37.4%)	12 [a] (31.6%)	
CDR≥1	64 (12.6%)	45 [a] (10.9%)	19 [b] (19.8%)		61 [a] (13.0%)	3 [a] (7.9%)	
MMSE	46 (9.1%)	36 [a] (8.7%)	10 [a] (10.4%)	0.606	43 [a] (9.1%)	3 [a] (7.9%)	0.796
GDS	157 (30.9%)	119 [a] (28.9%)	38 [b] (39.6%)	**0.041**	147 [a] (31.3%)	10 [a] (26.3%)	0.524
ADL – Dependent	29 (5.7%)	20 [a] (4.9%)	9 [a] (9.4%)	0.086	27 [a] (5.7%)	2 [a] (5.3%)	0.902
IADL – Dependent	163 (32.1%)	127 [a] (30.8%)	36 [a] (37.5%)	0.207	153 [a] (32.6%)	10 [a] (26.3%)	0.428
Neurocognitive disorder*							
NCD-normal	163 (62.9%)	139 [a](64.1)	24 [a] (57.1%)	0.085	149[a] (62.1%)	14 [a] (73.7%)	0.381
NCD-mild	61(23.6%)	46 [a] (21.2%)	15 [b] (35.7%)		59 [a] (24.6%)	2 [a] (10.5%)	
NCD-Major	35 (13.5%)	32 [a] (14.7%)	3 [a] (7.1%)		32 [a] (13.3%)	3 [a] (15.8%)	

Abbreviations: *APOE*=Apolipoprotein E; ε: alleles; CDR: Clinical Dementia Rate; MMSE: Mini Mental State Examination; ADL: Activities Daily Life; IADL: Instrumental Activities Daily Life; DSM-5: Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition. CDR- Clinical Dementia Rate; MMSE- Mini Mental State Examination; GDS-Geriatric Depression Scale; NTC-normal- Neurocognitive disorder normal; NCD-mild-Neurocognitive disorder mild: NCD-major- Neurocognitive disorder major. Superscripts letters: [a,b]: the same letter means that don´t have statistical difference between class. The different class means that there is statistical difference between classes. In bold p-value<0.05. The patients with depression and with inconclusive diagnostic were excluded. To Dementia (DSM-5), the total N is not 508. Total "N" is 259. There is statistical significance in Dementia diagnostic based in DSM – V relative to allele ε4 *APOE* genotyping and Neurocognitive disorder mild. There is not statistical significance to alleleε2 and Dementia criteria. There is not statistical significance in depressive cases. In bold, the value of p-value<0.05.

Regarding the associations between *APOE* genotype and cognition, the percentage of individuals with moderate to severe cognitive decline based on the CDR scores is greater in ε4 carriers (p=0.035) [201]. This is consistent with other literature reports. None of the *APOE* genotypes associate with instrumental activities of life, IADL or with ADL. Of note, no correlations between *APOE* genotype and MMSE are observed. Another aspect monitored includes geriatric depression determined by applying the GDS scale (GDS≥5); high GDS scores associate significantly (Table 35) with *APOE ε4* carriers (p-value=0.041). With the application of DSM-5 criteria for neurocognitive disorders, no significant correlations with APOE are evident. It could be that the N is relatively small.

4.3.3 Association of *APOE* Alleles with Comorbidities

All volunteers were scored for the presence of other diseases; the most representative are shown in table 36. *APOE ε4* carriers significantly associate with dyslipidaemia (p<0.05). With moderate statistical significance, there is a correlation with respiratory disease and *APOE ε4* and CVD and DM with *APOE ε2*. None of the other comorbidities investigated significantly associated with *APOE ε2* andε4 carriers or non-carriers.

Table 38 Clinical features of the pcb-cohort and correlations with *APOEε4* and *APOEε2*

Comorbidities	N (%) N=508		*APOEε4-* N=412		*APOEε4+* N=96		p-value	*APOEε2-* N=470		*APOEε2+* N=38		p-value
HTA	311	61.2%	256[a]	(62.1%)	55[a]	(57.3%)	0.380	291[a]	(61.9%)	20[a]	(2.6%)	0.259
DYS	302	59.4%	235[a]	(57.0%)	67[b]	(69.8%)	**0.022**	287[a]	(61.1%)	15[b]	(39.5%)	**0.009**
OA	268	52.8%	216[a]	(52.4%)	52[a]	(54.2%)	0.759	248[a]	(52.8%)	20[a]	(52.6%)	0.987
CVD	277	54.5%	219[a]	(53.2%)	58[a]	(60.4%)	0.198	262[a]	(55.7%)	15[a]	(39.5%)	0.053
DEP	159	31.3%	130[a]	(31.6%)	29[a]	(30.2%)	0.798	146[a]	(31.1%)	13[a]	(34.2%)	0.687
GID	131	25.8%	109[a]	(26.5%)	22[a]	(22.9%)	0.475	120[a]	(25.5%)	11[a]	(28.9%)	0.643
GUD	113	22.2%	88[a]	(21.4%)	25[a]	(26.0%)	0.320	105[a]	(22.3%)	8[a]	(21.1%)	0.854
DM	100	19.7%	83[a]	(20.1%)	17[a]	(17.7%)	0.589	97[a]	(20.6%)	3[a]	(7.9%)	0.057
RESP	81	15.9%	72[a]	(17.5%)	9[a]	(9.4%)	**0.051**	76[a]	(16.2%)	5[a]	(13.2%)	0.626
HEMATO	53	10.4%	45[a]	(10.9%)	8[a]	(8.3%)	0.455	48[a]	(10.2%)	5[a]	(13.2%)	0.568
ONCO	28	5.5%	22[a]	(5.3%)	6[a]	(6.3%)	0.725	24[a]	(5.1%)	4[a]	(10.5%)	0.159
NEURO	22	4.3%	18[a]	(4.4%)	4[a]	(4.2%)	0.930[b]	20[a]	(4.3%)	2[a]	(5.3%)	0.769

Abbreviations: *APOE*-apolipoprotein; ε-allele of *APOE*; (-) without characteristic; (+) with the characteristic; SD-Standard Deviation; HYP=Hypertension Arterial; DYS-Dyslipidaemia; OA-Osteoarthicular disease; CVD-Cardiac and vascular disease; DEP-Depression; GID-Gastrointestinal disease; GUD-Genitourinary disease; DM-Diabetes Mellitus; RESP-Respiratory disease; HEMATO-Hematologic disease; ONCO-Oncology disease; NEURO-Neuropathologies; ALCOHOL-Alcohol Excessive Use. Data are presented as N (%) and % is expressed as a function of the total in each of the *APOE* groups. Statistical test used: χ^2=Chi square test; Superscripts letters: [a,b] The same subscript letter denotes a subset of MMSE categories whose column proportions do not differ significantly from each other at the p 0.05 level. Different subscript letters denote column proportions that differ significantly from each other at the p 0.05 level. Tests assume equal variances. Tests are adjusted for all pairwise comparisons using the Bonferroni correction. In bold, the value of p-value<0.05.

Patients with DYS are *APOE4* carriers, in a higher statistical significance percentage (57.0% vs 69.8%), compared to non-*APOE4* carriers (p=0.022). Regarding patients with RESP, *APOE4* carrier patients are in a lower proportion than non-carriers with statistical significance (17.5% vs 9.4%. p=0.051).

For patients with CVD, *APOE2* carriers have a statistically higher percentage (55.7% vs 39.5%), compared to non-*APOE2* carriers (p=0.053). It is also noted that, in relation to patients with DM, *APOE2* carriers have a higher percentage (20.6% vs 7.9%), compared to non-*APOE2* carriers, with moderate statistical significance (p=0.057).

Results 4.4
Inappropriate Medication Usage in the pcb-Cohort

4.4 Inappropriate Medication in the pcb-Cohort

As briefly discussed in the introduction, polypharmacy is the concurrent use of multiple medications and it can be a problem particularly relevant in the older populations. Thus, medication usage was addressed in this study; relevant data was available for 361 participants. Within the pcb-Cohort, the total number of medications used is 2306. The average number is 6.39±3.55; with a minimum=0 and a maximum=19. For men the average is 4.96±2.80 and for women 7.04±3.60 (p<0.001). Only 5.5% (N=20) of patients are classified as no polypharmacy; 28 % (N=101) are classified as polypharmacy minor (using 2 to 4 chronic medications) and 66.5% (N=240) are polypharmacy major (using more than 5 chronic medications).

4.4.1 Potentially Inappropriate Medication

4.4.1.1 Table 1 Beers Criteria: Potentially Inappropriate Medication Use in Older Adults in the pcb-Cohort

The data collected was organized bearing in mind the Beers Criteria (Annex I- Supplementary table 1- Table I of the Beers Criteria AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults – PIM1). It is evident that, in the pcb-Cohort, 190 (52.6%) patients 65 years old or more, are not using any medication from the list of PIMs. The 171 break down as follows: 104 (29.6%) patients using one PIM1; 53 (14.7%) patients using two PIM1; 9 (2.5%) patients using three PIM1 and 2 patients (0.6%) using four PIM1. The prevalence of medication classified as PIM1 (Table I- Beers Criteria) is shown in table 39. The most frequently used medications include Benzodiazepines (short and intermediate acting) 19.4% (N=70); other Benzodiazepines 16.1% (N=58); Benzodiazepines (long-acting) 8.6% (N=31); conventional and atypical Antipsychotics 6.0% (N=22); and Non-steroidal Anti-inflammatory drugs (oral) 6.0% (N=22).

Table 39 Frequency of Potentially Inappropriate Medication Use in Older Adults in the pcb-Cohort

Drugs PIM1	N	%
Benzodiazepines Short- and intermediate-acting	70	19.4%
Other Benzodiazepines	58	16.1%
Benzodiazepines Long-acting	31	8.6%
Non-COX-selective (NSAIDs oral)	22	6.0%
No benzodiazepine Hypnotics	18	5.0%
Antipsychotics. first(conventional) and second(atypical) generation	16	4.4%
Antithrombotic	15	4.2%
Antiarrhythmic drugs (Class Ia. Ic. III)	14	3.9%
Tertiary TCAs. alone or in combination	11	3.1%
Others Cardiovascular disease drugs	2	0.6%
Pain medications	2	0.6%
First-generation antihistamines	1	0.3%
Antiparkinson agents (Benzitropine)	1	0.3%

Abbreviations: COX-cyclooxygenases; NSAIDs-Non steroids anti-inflammatory drugs; TCAs-tricyclic antidepressants. The medications classified in Table I of Beers Criteria (PIM1) are presented in decreasing order of usage. % is relative to total number of patients (N=361). In the class of Benzodiazepines Short and intermediate acting the drugs are: Alprazolam N=31 (8.6%). Estazolam N=1 (0.3%). Lorazepam N=35 (9.7%). Oxazepam N=1 (0.3%) and association among these medications N=2 (0.6%); In the class of Benzodiazepines Long-acting drugs are: Chlorazepate N=6 (1.7%). Clonazepam N=1 (0.3%). Diazepam N=21 (5.8%). Flurazepam N=3 (0.8%); Other Benzodiazepines are: Bromazepam N=23 (6.4%). Cloxazolam N=8 (2.2%). Mexazolam N=10 (2.8%). Brotizolam N=1 (0.3%). Midazolam N=1 (0.3%). Ethyl Loflazepate N=5 (1.4%). Clobazam N=7 (1.9%).

Relative to PIM1 there are some medications with a low number of users the cardiovascular drug of low usage in the pcb-Cohort is Spironolactone>25mg/day, N=2. The low usage pain medication (Meperidine, Indomethacin, Ketorolac, Pentazocine) has N=2 and the first-generation Antihistamines N=1 and the antiparkinsonian agents (Benztropine) has an N=1. The other classes of medications of the Table one of Beers Criteria do not have any cases. The other drugs not included in the table, because they do not constitute PIM are (although the patient was taking the medication, it had no criteria for PIM): Barbiturates (Phenobarbital) N=1 (0.3%), Amiodarone N=8 and Sotalol N=5, and Endocrine Drugs (estrogens with or without progestin N=2 (0.6%) and insulin as sliding scale N=7 (1.9%)). The other classes of medications of the Table one of Beers Criteria do not have any cases.

4.4.1.2 Table 2 Beers Criteria: Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome

Beers Table 2 (see Annex I) addresses the interactions of the drugs with diseases or with syndromes: Beers Criteria for PIM Use in Older Adults Due to Drug-

Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome (PIM2). The pathologies that must be considered from Table 2 Beers Criteria (see Annex 1 – Supplementary Table 2) are:

- Cardiovascular: heart failure and syncope;
- Central Nervous System: seizures or epilepsy, delirium, dementia syndrome, falls, insomnia, Parkinson's disease;
- Gastrointestinal Tract: constipation, gastric or duodenal ulcer; and Urinary Tract / Kidney: chronic renal failure stage IV or V. or urinary tract symptoms/benign prostatic hyperplasia stress urinary incontinence.

Table 40 describes the application of Table 2 of the Beers Criteria in patients of the pcb-Cohort. In the pcb-Cohort, the total number of patients in this study is 361. There are 27 patients with heart failure diagnosis; 78 patients with cognitive impairment/dementia based on DSM-5; 6 with Parkinson disease; 46 with a history of gastric or duodenal ulcers and 4 with chronic kidney disease stages IV or V (see Table 40).

Table 40 Beers Criteria for PIM use in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (PIM2) applied to the pcb-cohort

PIM2	Medication	N	%
Heart failure (N=27)	Not medicated with PIM	20	74%
	Diltiazem	5	18.5%
	Verapamil	2	7.5%
Dementia & Cognitive Impairment			
NCD-mild (N=48)	Not medicated with PIM	44	91.7%
	Benzodiazepines	3	6.2%
	Combination	1	2.1%
NCD-major (N=25)	Not medicated with PIM	20	80%
	Benzodiazepines	1	4.0%
	Zolpidem	1	4.0%
	Antipsychotics	3	12.0%
Parkinson's disease (N=6)			
	Not medicated with PIM	4	66.6%
	All antipsychotics	1	16.7%
	Antiemetic (metoclopramide, prochlorperazine, promethazine)	1	16.7%
History of gastric or duodenal ulcers (N=87)	Not medicated with PIM	65	74.7%
	Non-COX2 selective NSAIDs	22	25.3%
Chronic Kidney disease stages IV or V (N=4)	Not medicated with PIM	3	75%
	NSAIDs	1	25%

Abbreviations: PIM-Potentially Inappropriate medication use; NCD-Neurocognitive disorder (mild or major); DSM-5- DSM-The Diagnostic and Statistical Manual of Mental Disorders; COX2-Cyclooxygenase 2; NSAIDs-Non-steroids anti-inflammatory drugs; Note: % is based in subtotal indicate in first columns.

In the first group (heart failure), there are 5 patients using Diltiazem and 2 are using Verapamil. These two drugs are considered inappropriate when used in patients have heart failure pathology. These drugs must be avoided because they have a potential to promote fluid retention and/or exacerbate heart failure.

Table 40 also shows the results relative the patients with cognitive impairment/dementia. In patients above 65 years older, regarding dementia, a total of 108 (29.9%) no have syndrome or disease and patients have normal cognitive performance based in DSM-5, and 73 have history of neurocognitive disorder (NCD-mild=48 and NCD-major=25). Of these, 64 (44NCD-mild + 22NCD-major) (87.6%) patients are not using PIM2; 1 patient with NCD-major use Benzodiazepines; 1 NCD-major is using Zolpidem; 3 NCD-major is using combinations of the different classes already referred. There are 3 NCD-mild use benzodiazepines and 1 NCD-mild is using combinations of the different classes already referred. Relative to these drugs, antipsychotics should be avoided in patients with cognitive impairment because they

increase the risk of stroke and increase the mortality among patients. They can only be administered if non-pharmacological options for treating behavioural changes of dementia are unsuccessful and the patient poses a threat to her/himself and others

In the pcb-Cohort there are 6 patients with a diagnosis of Parkinson's disease (prevalence of Parkinson disease is of 1.7% in patients above 65 years old). 4 (1.1%) who have no reports of PIM. 1 (0.3%) using Antipsychotics and 1 (0.3%) using an Antiemetic (Table 40). These drugs must be avoided because they are dopamine receptor antagonists with the potential to worsen parkinsonian symptoms.

In pcb-Cohort, 87 patients above 65 years old have a history of gastric or duodenal ulcers. These patients 22 (0.6%) are using non-COX2 selective NSAIDs (Table 40). These drugs should also be avoided given that they may exacerbate existing ulcers or cause new/additional ulcers. Alternative drugs can be considered and if these are not effective a gastro protective agent (proton-pump inhibitor or misoprostol) may be considered. In case of chronic diagnosis of Kidney disease, there are 4 patients. And 1 (25%) is using NSAIDs (Table 40). These drugs must be avoided because they may increase the risk of kidney injury.

Some information is not represented in Table 40, essentially because there are no cases of PIM. These include:

- Lower urinary tract symptoms or benign prostatic conditions, with 31 cases of hyperplasia): anyone use PIM
- Chronic seizures or epilepsy: 20 cases, no use PIM;
- Insomnia: 14 cases, no use PIM;
- stress or mixed urinary incontinence in women: 8 cases, no use PIM;
- Chronic constipation: 6 cases, no use PIM;
- Urinary incontinence in women: 5 cases, no use PIM;
- Syncope: 1 case, no use PIM
- Delirium: anyone with this diagnostic
- History of fall or fractures: anyone with this diagnostic.

4.4.1.3 Table 3 Beers Criteria: Potentially Inappropriate Medications to Be Used with Caution in Older Adults

Table 3 of the Beers Criteria (Annex 1 – Supplementary table 3) for Potentially Inappropriate Medications addresses medications to be used with Caution in Older Adults (PIM3), it is designed for individuals that are more than 75 or 80 years old (depends on the drug). The drugs with which doctors should be particularly vigilant are Aspirin, Dabigatran, Prasugrel, Antipsychotics, Carbamazepine, Carboplatin and Cisplatin, Mirtazapine and Serotonin, Noradrenalin reuptake inhibitors, Selective Serotonin Reuptake Inhibitors, Tricyclics antagonists, Vincristine and Vasodilators. To apply Table 3 of the Beers Criteria, it is necessary to remember that we are dealing with patients that are more than 75 or 80 years older. In the pcb-Cohort there are 137 individuals over 75 years and 61 individuals over 80 years.

Aspirin for primary prevention of cardiac events should be used with caution in adults' ≥80 years old; there is a lack of evidence of benefit versus risk in individuals ≥80 years old. Likewise, Dabigatran must be used with caution in adults ≥75 years old, in cases where individuals have a Creatinine Clearance (CrCl) rate less than 30 mL/min. In these cases, the risk of bleeding is greater in comparison to Warfarin. Furthermore, there is a lack of evidence for efficacy and safety in patients with CrCl rate<30 mL/min. Prasugrel must also be used with caution in adult's ≥75 years old, because it presents a greater risk of bleeding in older adults; risk may be offset by benefit in highest risk older patients (e.g. those with prior myocardial infarction or diabetes). Also, vasodilators must be used with caution given that they may exacerbate episodes of syncope in individuals with a history of syncope.

Care must also be taken with drugs that may exacerbate or cause SIADH (Secretion Inappropriate Anti Diuretic Hormone) or hyponatremia. A good recommendation is to monitor sodium levels closely when starting or changing medication dosages in older adults and to bear in mind that these individuals have increased risks of suffering adverse drug effects. Drugs deserving attention are: Antipsychotics, Carbamazepine, Carboplatin, Cisplatin, Mirtazapine, SNRIs, SSRIs, TCAs and Vincristine. Thus, these drugs are included in Table 3 of the Beers Criteria. and

referred to as drugs that should be used with caution in patients above 80 or 75 years old as they may cause SIADH [165].

Relative to patients over 80 years, 8 (13.2%) are taking Aspirin to prevent cardiac events (see Table 3 Beers Criteria – Annex I- Supplementary table 3). Regarding Dabigatran, in 2012, patients were not using this drug, as in Portugal it had not yet been approved for use by the national regulatory agency. In the pcb-Cohort Prasugrel is also not being taken by any of the participants.

The other drugs from Table 3 of the Beers Criteria (Annex I – Supplementary table 3) are psychiatric drugs that may exacerbate or cause SIADH or Hyponatremia.

Table 41 show the results of Table 3 of Beers Criteria in pcb-Cohort.

Table 41 Table 3 of Beers Criteria applied to the pcb-Cohort

Medication		N	%
Aspirin* (N=62)	Not medicated with PIM	53	86.8%
	Use	8	13.2%
Cause SIAHD/Hyponatremia** (N=111)	Not medicated with PIM	250	69.3
	Antipsychotics	7	1.9
	SNRIs	2	0.6
	SSRIs	57	15.8
	TCAs	19	5.3
	Combinations	26	7.2
Vasodilators** (N=92)	Not medicated with PIM	269	74.5%
	Use	92	25.5%

*Patients 80 years old or more (N=61). In this case, % is based in N=61 **Patients 65 years old or more (N=361). % is based in N=361. Abbreviations: SNRIs-Serotonin Noradrenalin Receptors Inhibitors; SIAHD-Secretion Inappropriate of Antidiuretic Hormone; SSRIs-Serotonin Selective Receptors Inhibitors; TCA-Tricyclics Antidepressant; Association-Association of at least two drugs in this group of the drugs that cause SIAHD or Hyponatremia; There are no cases of other drugs that can cause SIAHD: Carbamazepine, Carboplatin, Cisplatin and Vincristine.

In the study sample, and about 250 (69.3%) patients are not using any of these drugs and 111 (30.7%) are (Table 41). Additionally, 7 (1.9%) patients are using

Antipsychotics (Table 37). 2 (0.6%) are using SNRIs (Serotonin Noradrenalin Receptors Inhibitors), 57 (15.8%) are using SSRI (Serotonin Selective Receptors Inhibitors), 19 (5.3%) are using TCAs (TCA=Tricyclic's Antidepressants) and 26 (7.2%) patients are using combinations of these psychiatric drugs. Curiously in the pcb-Cohort the greater use of PIM3 is vasodilators, where 269 (74.5%) patients do not take it while 92 (25.5%) patients do.

4.4.2 Association between Sociodemographic Characteristics with Polypharmacy and PIM1

PIM1 prevalence with respect to sociodemographic characteristics was analysed (Table 42). In the pcb-Cohort (N=361 have medication related information available), the prevalence of polypharmacy is 66.5% (240/361) in patients over 65 years of age. The polypharmacy affected 73.4 (182/248) % of women and 51.3% (58/113) of men; these differences are statistically significant (p<0.001). The prevalence of non-polypharmacy is greater in the comparatively younger age group; of 65-74 years: 37.6% (85/226) when compared to the age group over 75, 73.3% (99/135). Regarding individuals with or without polypharmacy there is a statistical difference between mean of age (71.5 vs 73.9, Table 38).

Non-polypharmacy patients have higher monthly incomes: the proportion of non-polypharmacy is higher in patients who earn more than the minimum wage, while the polypharmacy ratio is lower in patients who earn more than a minimum wage (37% versus 63%). These differences have statistical significance; patients with polypharmacy have a lower average number of years of education. The other sociodemographic characteristics did not have statistical significance.

Regarding the use of inappropriate medication, based on Beers Criteria for PIM1 (Table 42), the proportion of women using PIM1 is significantly higher (p-value 0.004). Other significantly different characteristics with respect to PIM1 are monthly income and years of study p-value=0.039 and p-value=0.045, respectively. The other socio-demographic characteristics did not present significant differences between the two groups (use or not of PIM1).

Table 42 Sociodemographic characteristics in polypharmacy and PIM1

Demographics Characteristics	N (%)	Polypharmacy			PIM1		
		PP- (N=120)[1]	PP+ (N=241)[1]	p-value	PIM1- (N=190)[1]	PIM1+ (N=171)[1]	p-value
Gender							
Male	113 (31.3%)	55[a] (45.5%)	58[b] (24.2%)	**<0.001**[2]	72[a] (37.9%)	41[a] (28.0%)	**0.004**[2]
Female	248 (68.7%)	66[a] (54.5%)	182[b] (75.8%)		118[a] (62.1%)	130[a] (72.0%)	
Age							
[65-74]	226 (62.6%)	85[a] (70.2%)	141[b] (58.8%)	**0.033**[2]	122[a] (64.2%)	104[a] (60.8%)	0.506[2]
[≥ 75]	135 (37.4%)	36[a] (29.8%)	99[b] (41.3%)		68[a] (35.8%)	67[a] (39.2%)	
Age (years) Mean ± SD	73 ± 6.2	71.5 ± 5.4[a]	73.9 ± 6.4[b]	**0.001**[3]	73 ± 6.3[a]	73.2 ± 6[b]	0.706[3]
Marital Status							
Partner[4]	241[a] 66.8%)	87[a] (71.9%)	154[a] 64.2%)	0.141[2]	131[a] (68.9%)	110[a] (64.5%)	0.141[2]
Other	120 33.2%)	34[a] (28.1%)	86[a] (35.8%)		59[a] (31.1%)	61(35.5%)	
Living Arrangement							
Alone	80 (22.2%)	26[a] (21.5%)	54[a] (22.5%)	0.827[2]	36[a] (16.8%)	44[a] (28%)	0.121[2]
Accompanied	281 77.8%)	95[a] (78.5%)	186[a] (77.5%)		154[a] (83.2%)	127[a] (72%)	
Professional Status							
Active	58 (16.1%)	13[a] (10.7%)	45[a] (18.8%)	0.147[2]	32[a] (55.2%)	26 (13.1%)	0.175[2]
Retired	300 83.1%)	107[a] (88.4%)	193[a] (80.4%)		158[a] (52.7%)	142 (86.0%)	
Unemployed	3 (0.8%)	1[a] (0.8%)	2[a] (10.8%)		0[a] (0.0%)	3 (0.9%)	
Monthly Income				0.054[2]			**0.039**[2]
≤ 1[5]	126 34.9%)	34[a] (27.0%)	92[b] (73.0%)		57[a] (30%)	69 (36.4%)	
> 1[5]	235 65.1%)	87[a] (37.0%)	148[b] (63.0%)		133[a] (70%)	102 (63.6%)	
Education Level							
0-2[6]	41 (11.4%)	12[a] (29.3%)	29[a] (12.1%)	**0.005**[2]	17[a] (8.9%)	24 (10.2%)	0.090[2]
3-6[6]	272 75.3%)	83[a] (30.5%)	189[a] (78.8%)		142[a] (74.7%)	130 (78.5%)	
≥ 7[6]	48 (13.3%)	26[a] (54.2%)	22[a] (9.2%)		31[a] (16.3%)	17 (10.3%)	
Years of Studies (Mean ± SD)	4.5 ± 3.4	5.2 ±3.8[a]	4.1 ± 3.1[b]	**0.006**[3]	4.8 ± 3.5	4.1 ± 3.1[b]	**0.045**[3]

Superscripts letters: [a,b] The same subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level.
Abbreviations: SD-Standard Deviation; PP- use less than 5 medications; PP+ Polypharmacy (≥5 medications).
NOTE:

1. Data presented as N (%) and % is expressed % as a function of the total in each of the PIM or Polypharmacy group or mean ± standard deviation.
2. Statistical test: χ^2 = Chi square test
3. Statistical test: Test *t* student;

4.4.3 Association between Comorbidities with Polypharmacy and PIM1

The results of comparing comorbidities, polypharmacy and PIM1 are shown in Table 39. In the pcb-Cohort the mean number of co-morbidities is higher in both cases of polypharmacy and in cases of PIM1. Patients with polypharmacy have a higher average number of comorbidities namely Hypertension, Dyslipidaemia, Cardiac and vascular disease, Osteoarticular disease, Depression, Gastrointestinal disease and Haematology pathology.

Patients using inappropriate medication, based on PIM1, are mostly those with a history of Depression, Cardiac and vascular Disease and Gastrointestinal disease; the latter are statistically significant. Remember that we have 366 patients over 65 years, but the medication data were only possible at 361. The table percentages are based on the 361 individuals of the pcb-Cohort, as explained above (Table 43).

Table 43 Bivariate correlation between comorbidities and polypharmacy and PIM1

Comorbidities	N=361	PP- N=120	PP+ N=241	p-value	PIM - N=190	PIM + N=171	p-value
Number of Disease	3.2 ± 1.6	2.4 ± 1.3	3.7 ± 1.6	**<0.001**[2]	3 ± 1.4	3.5 ± 1.7	**0.004**[2]
HTA	247 (68.4%)	65[a] (53.7%)	182[b] (75.8%)	**<0.001**[3]	124[a] (65.3%)	123[a] (71.9%)	0.174[3]
DYL	225 (62.3%)	63[a] (52.1%)	162[b] (67.5%)	**0.004**[3]	119[a] (62.6%)	106[a] (62.0%)	0.900[3]
OA	201 (57.7%)	56[a] (46.3%)	145[b] (60.4%)	**0.011**[3]	101[a] (53.2%)	100[a] (58.5%)	0.309[3]
CVD	216 (59.8%)	54[a] (44.6%)	162[b] (67.5%)	**<0.001**[3]	102[a] (53.7%)	114[b] (66.7%)	**0.012**[3]
DEP	106 (29.4%)	23[a] (19.0%)	83[b] (34.6%)	**0.002**[3]	44[a] (23.2%)	62[b] (36.3%)	**0.006**[3]
GID	108 (29.9%)	25[a] (20.7%)	83[b] (34.6%)	**0.006**[3]	45[a] (23.7%)	63[b] (36.8%)	**0.006**[3]
GUD	87 (22.4%)	21[a] (17.4%)	61[a] (25.4%)	0.084[3]	39[a] (20.5%)	43[a] (25.1%)	0.296[3]
DM	76 (21.1%)	21[a] (17.4%)	55[a] (22.9%)	0.221[3]	38[a] (20.0%)	38[a] (22.2%)	0.605[3]
RESP	64 (17.7%)	15[a] (12.4%)	49[a] (20.4%)	0.060[3]	35[a] (18.4%)	29[a] (17.0%)	0.716[3]
HEMATO	45 (12.5%)	6[a] (5.0%)	16[a] (6.7%)	0.522[3]	13[a] (6.8%)	9[a] (5.3%)	0.531[3]
ONCO	22 (6.1%)	6[a] (5.0%)	39[b] (16.3%)	**0.002**[3]	23[a] (12.1%)	22[a] (12.9%)	0.827[3]
NEURO	18 (5.0%)	4[a] (3.3%)	14[a] (5.8%)	0.298[3]	8[a] (4.2%)	10[a] (5.8%)	0.475[3]
ALCOOL	7 (1.9%)	4[a] (3.3%)	3[a] (1.3%)	0.181[3]	4[a] (2.1%)	3[a] (1.8%)	0.809[3]

Abbreviations: PP-: use less than 5 medications; PP+: Polypharmacy (≥ 5 medications); PIM1: The table 1 of 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults; NC: number of comorbidities. (-) means absence of characteristic and (+) Means presence of the characteristic

NOTE: Data presented as N (%) and % is expressed as function of the comorbidities.

1. Statistical test: Test *t* student;
2. Statistical test: χ^2 = Chi square test

Superscripts letters [a, b]: The same subscript letter denotes a subset of categories whose column proportions don not differ significantly from each other at the 0.05 level. Different subscript letters denote column proportions which differ significantly from each other at the 0.05 level

4.4.4 Association among PIM1 and PP with Cognitive Evaluation

This session describes the correlation between the cognitive performance of pcb-Cohort users with PIM1 and Polypharmacy. Table 44 shows these correlations. Regarding CDR, patients with no cognitive impairment showed a lower proportion of polypharmacy and PIM1, with statistical significance (p<0.05). Patients with CDR=0.5, on the other hand, already present a higher proportion of polypharmacy and PIM, although still with no statistical significance. Patients with cognitive impairment clearly show a higher proportion of PIM1 and polypharmacy with statistical significance.

When DSM-5 is applied, identical behaviour is observed. Patients without cognitive impairment have a lower proportion of polypharmacy and PIM (Table 40). Statistical significance is not observed for NCD-mild and NCD-major. However, it is observed that patients classified as possible cases of depression, present a higher proportion of use of PIM and polypharmacy.

Table 44 Correlation of cognitive performance with PIM1 and polypharmacy in the pcb-Cohort

Cognitive Parameters	N=361	PP- N=120	PP+ N=241	p-value	PIM - N=190	PIM + N=171	p-value
Clinical Dementia Rate							
CDR=0	168	106[a] (55.8%)	62[b] (36.3%)		69[a] (57.0%)	99[b] (41.3%)	
CDR=0.5	170	63[a] (33.2%)	71[a] (41.5%)	**<0.001**	40[a] (33.1%)	94[a] (39.2%)	**0.008**
CDR≥1	23	21[a] (11.1%)	38[b] (22.2%)		12[a] (9.9%)	47[b] (19.6%)	
DSM-5							
NCD-normal	108	78[a] (41.1%)	30[b] (17.5%)		50[a] (41.3%)	58[b] (24.2%)	
NCD-mild	48	24[a] (12.6%)	24[a] (14.0%)	**<0.001**	18[a] (14.9%)	30[a] (12.5%)	**0.002**
NCD-major	25	13[a] (6.8%)	12[a] (7.0%)		9[a] (7.4%)	16[a] (6.7%)	
Possible cases of Depression	180	75[a] (39.5%)	105[b] (61.4%)		44[a] (36.4%)	136[b] (56.7%)	

Abbreviations: CDR-Clinical Dementia Rate; DSM-5-PP-: use less than 5 medications; PP+: Polypharmacy (≥ 5 medications); PIM1: The table 1 of 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults; NC: number of comorbidities. (-) means absence of characteristic and (+) Means presence of the characteristic. Note: Values in the same row and subtable not sharing the same subscript are significantly different at p<0.05 in the two-sided test of equality for column proportions. Cells with no subscript are not included in the test. Tests assume equal variances. Tests are adjusted for all pairwise comparisons within a row of each innermost sub table using the Bonferroni correction.

4.4.5 Multivariate Analyses: Factors Associated with Polypharmacy and PIM1

Multivariate analysis was subsequently carried out (Table 41), using the Logistic Regression Model. Relative to Logistic Regression for polypharmacy to validate the model, the R^2 measure was as proposed by Nagelkerkethe [202]; has a score of 0.346 (Model Summary-2 log Likelihood=356.836), it has the Omnibus test χ2 (df 18)=103.650, p<0.001 and it has Hosmer and Lemeshow test χ2 (df 8)=4.403, p-value=0.819. The values validating the model for PIM1 are: the R^2 has a score of 0.253 (Model Summary-2 log Likelihood =423.641), the Omnibus test χ2 (df 18)=75.811, p<0.001 and Hosmer and Lemeshow test χ2 (df 8)=16.143, p-value=0.040. Relative to polypharmacy, the factors that were statistically significant in the multivariate analysis by logistic regression were (table 32): age over 75 with OR 1.9 (CI 95% 1.084-3.471, p-value 0.026); being female 2.042 (CI 95% 1.130-3.390, p-value 0.018); 3-6 years of education OR 2.6 (CI 95% 1.061-6.486, p-value 0.037); Gastrointestinal disease OR 1.6 (CI 95% 0.936-2.768, p-value 0.085); Cardiac and vascular disease OR 2.09 (CI 95% 1.155-3.788, p-value=0.015); and potentially inappropriate medication use OR 4.5 (CI 95% 2.587-8.038, p-value<0.001).

Relative to results of Logistic Regression to PIM1, the factors that significantly contribute to potentially inappropriate medication use are: Dyslipidaemia OR 1.6 (95%CI 0.935-2.962, p-value=0.083); Cardiac and vascular diseases OR 1.6 (95%CI 0.942-2.919, p-value=0.080); Respiratory diseases OR 1.6 (95%CI 0.930-3.098, p-value=0.085); cognitive impairment based DSM-5 (neurocognitive disorder major and mild) OR 2.6; 95% CI 1.245-5.561, p-value=0.011; and with the additional presence of polypharmacy (OR 4.5; 95% CI 2.623-8.053, p-value<0.001).

Table 45 Multivariate analyses based on logistic regression to polypharmacy and PIM1

Characteristics	Polypharmacy				PIM1			
	p-value	OR	CI (95%)		p-value	OR	CI (95%)	
≥75 years old	**0.026**	1.940	1.084	3.471	0.742	1.090	0.652	1.823
Female	**0.018**	2.042	1.130	3.690	0.333	1.319	0.753	2.312
0-2 years of Literacy*	**0.008**				0.724			
3-6 years of Literacy	**0.037**	2.623	1.061	6.486	0.421	0.719	0.322	1.605
≥7 years of Literacy	0.955	0.969	0.328	2.869	0.581	0.751	0.271	2.079
DM	0.862	1.062	0.540	2.087	0.483	1.230	0.689	2.195
HYP	0.444	0.812	0.476	1.384	0.460	1.199	0.741	1.939
DYS	0.130	1.594	0.872	2.916	0.083	1.664	0.935	2.962
GID	0.085	1.610	0.936	2.768	0.686	1.106	0.678	1.804
CVD	**0.015**	2.092	1.155	3.788	0.080	1.658	0.942	2.919
RESP	0.185	1.619	0.794	3.300	0.085	1.697	0.930	3.098
OA	0.449	1.250	0.701	2.229	0.478	0.826	0.486	1.402
CDR=0*	0.708				0.752			
CDR=0.5	0.828	1.088	0.509	2.325	0.673	1.153	0.595	2.233
CDR≥1	0.407	2.487	0.288	21.449	0.456	1.761	0.398	7.798
NCD	0.980	1.010	0.448	2.280	**0.011**	2.643	1.245	5.610
Depressive cases	0.402	1.512	0.575	3.974	0.188	1.638	0.786	3.413
Polypharmacy					**<0.001**	4.596	2.623	8.053
PIM1	**<0.001**	4.560	2.587	8.038				

Abbreviations: OR-Odds Ratio; CDR-Clinical Dementia Rate; PIM1: Potentially Inappropriate Medication based in table 1 of Beers Criteria. HYP- Hypertension; DYS-Dyslipidemia; OA-Osteoarthicular; CVD-Cardiac and vascular disease; GID-Gastrointestinal disease; DM-Diabetes Mellitus; RESP- Respiratory disease. In bold, the p-value with statistical significance. * reference Class to calculate OR to variable literacy and CDR. Variable(s) entered in Logistic Regression ENTER methods: Age (group), Gender, Literacy, Diabetes Mellitus, Hypertension, Dyslipidemia, Gastrointestinal disease, Cardiac and vascular disease, Respiratory disease, Neurodegenerative, Osteoarthicular, CDR, MMSE, polypharmacy, Neurocognitive disorder and depressive cases.

Therefore, polypharmacy is well associated with patients with more quality, with less literacy, and with cardiac or vascular disease as well as with the presence of inappropriate medication use. Regarding PIM1, this is well associated with NCD, and with moderate significance to cardiac and vascular and respiratory diseases.

CHAPTER 5

Discussion

5.1 Establishing the Study Group

At the onset of this thesis it was important to establish a study group. Bearing in mind that the fundamental concern was to contribute to identifying putative dementia and depression related cases in primary health care centres, a cohort based on individuals attending local health care facilities was established. The pcb-Cohort is an observational longitudinal study and represents an important contribution in the Aveiro region, at the level of primary health care centres. As previously mentioned, the Aveiro region has around 75.000 habitants. To determine the size of the study sample [176] for the Aveiro region, the number necessary is at least 480 individuals. In fact, the pcb-Cohort includes 590 individuals.

The main goal is to test tools to characterize the functional capacity and the prevalence of dementia and depression at the primary point of care. Given the pathologies involved participants recruited had to be at least 50 years old. Often the cut-off is 65 years for this type of study but given the intent to identify putative cases early on and to carry follow up studies participants recruited had to be at least 50 years old. Furthermore, information regarding medication usage in the study group was also collected. Other data collected included sociodemographic characteristics and clinical, information. Blood was collected to permit genotyping for the APOE.

It was the intent of this study to identify putative poor cognitive performance as early as possible. Also, for subsequent follow up studies, envisaged in the future, there will be increased opportunities to see how ageing affects cognitive capacities. Cognitive capacities were evaluated using the CDR and MMSE tests but to add further clinical relevance to the data collated the DSM-5 criteria were applied as already described in the results. It is not the intent of this study to profile the Portuguese population as addressed in other studies [180] or to accurately diagnose depression and dementia cases like AD. Dementia is a growing problem in modern societies so if putative cases can be identified early on and subsequently referred to specialised consultations this would contribute to efficiently dealing with such pathologies. Dementia impacted 46.8 million people worldwide in 2015, and this number is expected to almost double every 20 years [203].

5.1 Cognition based on CDR and DSM-5 in the pcb-Cohort

The CDR evaluation of the pcb-Cohort identified 12% (N=68) of the participants as having mild-to-severe cognitive deficits. Of these, 7 (10.3%) are <65 years old. These 7 participants have a high CDR score and are particularly young, they should therefore be closely monitored. With respect to cases of suspected cognitive deficits, scoring 0.5 on the CDR, there were another 64 subjects, again in the younger age group of 50–64 years. This also highlights the importance of including younger participants in the study. Overall, it is relevant to note that by applying the CDR, even in a primary care setting it is indeed possible to identify putative cases of cognitive deficits (Table 8) in both the younger and older participants.

In this study CDR scores were correlated with comorbidities in gender specific and in absolute terms. In both cases significant differences are evident between cognitive results and OA and GID. With women correlations were more evident with depression and hematologic diseases, whereas for men correlations are more evident with GUD and excessive use of alcohol (Tables 8 and 9). As with many other disease states, the concern with risk factors is paramount and the multivariate analysis characterizing cognitive alteration based on CDR, revealed the following to be risk factors: being female, having few years of literacy, exhibiting a degree of dependence, having a neuropathology, or a disease of the gastrointestinal tract and being a non APOE ε2 carrier.

When applying the DSM-5 criteria for neurodegenerative disorders, results were like those obtained when considering only the CDR data. Of all the participants, 189 have normal cognitive performance, 61 have NCD-mild, 36 have NCD-major and 282 were excluded because they are possible or confirmed cases of depression. The latter represents a prevalence of 12% cases (N=36) of dementia in the study population (NCD-major). Of the 36 individuals with NCD-major, around 28% are between 50-64 years old, 30% are 65-74 years old and 42% more than 75 years old. The percentage in the younger age group is only marginally lower when compared to

older individuals. This is a strong indicator for monitoring these younger individuals with respect to putatively developing dementia.

As with the CDR data, applying the DSM-5 criteria revealed that the risk factors associated with NCD are: the female gender, increasing age, few years of literacy, and being dependent. OA and GID still correlate although the latter in NCD-mild and neither hold in the multivariate analysis. The difference was investigated by comparing the data based on CDR and DSM-5 criteria (Table 46 below).

It can be observed that patients with normal performance in both assessment methods are 189. Also 9 patients with mild, moderate to severe cognitive impairment (CDR based) are assessed as NCD-mild because their IADL was not compromised. Encouragingly, there is an overlap of 12 patients with the same degree of severity in both methods. Also 24 users, although suspected, for the CDR, are already classified as NCD-major because they already have the IADL compromised.

Table 46 Correlation between number of patients with CDR and DSM-5 criteria

		DSM-5				Total
		NCD-Normal	NCD-mild	NCD-major	PCD	
CDR	CDR=0	189	0	0	112	301
	CDR=0.5	0	52	24	123	199
	CDR>=1	0	9	12	47	68
Total		189	61	36	282	568

Abbreviation: DSM-5- ; CDR-Clinical Dementia Rate; CDR=0- cognitive performance is normal; CDR=0.5-cognitive performance suspect; CDR≥1-cognitive performance mild, moderate, severe; NCD-Neurocognitive disorder; PCD-Possible cases of depression.

It is noteworthy that the number of patients classified as possible cases of depression, strongly impacts the results. Of the total group with depression (282), 123 scored CDR=0.5 and 47 cases with CDR≥1, this is a total of 170 participant lost from the study and of these although depressed they appear to also be cognitively compromised, particularly true for the 47 cases with CDR≥1. Nonetheless these patients were excluded to diminish selection bias when applying the DSM-5 criteria for NCD.

Regarding the application of CDR test as the main screening test, there are studies in Portugal that also use it for characterizing dementia. By consulting the

literature, it is possible to compare these results with studies that are ongoing. Namely, a prevalence study of dementia and depression at a national level: this is carried out by the 10/66 Dementia Research Group [204]. In this study evaluations include, cognitive deficit profiling based on a formal test, corroboration of cognitive and functional decline (by an informer), and a clinical interview, determining if a high probability of being a case of dementia exists. The methodologies used in this thesis are similar thus it will be interesting to compare the forthcoming data with that presented in this thesis.

When analyzing the determinant factors in the characterization of patients by both CDR and DSM-5, there is a clear overlap. Special attention should be given to the presentation of pathology of the gastrointestinal tract as a risk factor for cognitive impairment. This feature is statistically significant in the CDR assessment and with an increased proportion in the NCD-mild group; this will be further explored below.

5.1.1 Sociodemographic Risk Factors in Cognitive Impairment

Many of the risk factors for cognitive impairment identified above have already been reported in the literature.

Regarding age as a risk factor, in Portugal, there is a study called the Study of the Aging Profile of the Portuguese Population. In it the authors describe a statistically significant association between cognitive evaluation score and the age group, $p<0.001$. Namely in the 65-74 age group exhibits the lowest percentage of individuals with cognitive impairment (3.6%), followed by the age group of 55-64 years (3.9%), and the oldest age group of 75 years or older, present the highest percentage of individuals in an unfavorable situation (12.0%) [180]. This same study shows that the age group ≥ 75 years of age has a functional dependence about 2 times higher than the other age groups. The values in the work here presented are superior (globally CDR based prevalence 12% and NCD-major 12%) but this can be explained by the fact that the study group was based in primary health care centres. Of note studies have shown that Dementia prevalence can range from 5 to 10% among those aged≥65 years [8,206,207]. Regarding the CDR's performance in identifying these risk factors, the CDR can identify dementia conversion rates with age [37,208].

Another factor involved in cognitive change is literacy [84]. In the study of ageing in Portugal, it is reported that only 7.7% have completed school education for more than 12 years. These results are in line with national figures showing that about 23% have schooling of less than 3 years [180]. Having more years of literacy is described as a protective factor for dementia [84]; this holds true for the pcb-Cohort.

Another important factor in cognitive change is gender. Regarding the difference in the proportion of cases of dementia in women, the literature shows that, due to menopause and the consequent decline in estrogen levels, there is an increased risk of cognitive impairment and the prevalence of other diseases [190]. This is also reflected in the pcb-Cohort where women are 3.7 times more likely to have dementia compared to men (Table 18).

5.1.2 Comorbidities as Risk Factor in Cognitive Impairment

Dementia has previously been associated with several comorbid conditions [207]. For instance, diabetes is associated with an increased rate of cognitive decline [208]. There are several factors that may contribute to the increased risk for dementia in patients with diabetes: macrovascular and microvascular disease, genetic predisposition, hypertension, hypoglycaemia and hyperglycaemia, insulin resistance and hyperinsulinemia, chronic inflammation, dysregulation of the hypothalamic pituitary axis [209]. However, this correlation was not found in the pcb-Cohort.

Other comorbidities associated with dementia are hypertension. Likewise, many studies have shown that midlife hypertension is associated with increased dementia risk in later life [210]. A previous study in the Aveiro district [211] on patients in long-term facilities found that hypertension had a lower prevalence than that reported in the study here presented (41.3% vs 61.8%) [211] for the pcb-Cohort. The association between dementia and hypertension can be explained because blood pressure values: a high systolic BP (≥160 mm Hg) are associated with a greater dementia risk in the youngest group (65–74 years) [212]; a high diastolic BP (>90 mm Hg) is associated with a lower risk of developing dementia 6 to 9 years later [213]. In the pcb-Cohort the blood pressure was not performed. In future follow up studies, information regarding this parameter will be collected.

To our knowledge GID was correlated with high CDR scores for the first time in the pcb-Cohort. In the Aveiro district, a prevalence of GID 10% [211] has previously been described in an independent study. In the pcb-Cohort there are a 26.6% of GID cases, this is higher than that previously reported. In the pcb-Cohort these individuals with GID exhibit a higher risk of poor cognitive performance; there is a highly significant correlation between CDR≥0.5 and GID+.

It will be important to monitor these cases and address the issue of whether GID is a confounding factor, of relevance. GID has been associated with poor diet [214]. Hence, by analogy, the association of GID with high CDR scores supports the finding that a Mediterranean diet can be a protective factor for dementia [214,215]. In fact, the diet may affect the molecular basis for AD [22,215] including processes leading to plaque deposition [216]. Furthermore, GID is associated with ageing populations [217]. However, one cannot dismiss the possibility that medications used by the elderly patients may contribute to GID, and, in fact, an association between proton pump inhibitors (PPI study) and cognitive impairment has recently been reported [218,219]. The study design of this association of the use of proton inhibitory pump medications is different from the design of our study. In the PPI study, it is believed that the association may be due to inhibition of vitamin B12 absorption and increased deposition of beta-amyloid. It is true that the molecular nature of the association of gastrointestinal pathologies and cognitive impairment deserves further attention. However, this biomolecular study was not the focus of the study of this thesis. Nonetheless, it is particularly noteworthy that the enteric nervous system is as important as the central nervous system [217], since it is equally enervated and subject to the same neurotransmitter signalling cascades.

In pcb-Cohort the correlation between cognitive performance and disease of the respiratory tract was shown. In the above mentioned study in the Aveiro region, a prevalence of 6.4% of respiratory pathologies was observed [211]. Asthma in midlife and in late life appears to increase the risk of developing dementia and AD, but the physiopathology is as yet uncertain [220]. Another study showed that Chronic Obstructive Pulmonary Disease (COPD) is associated with cerebral small-vessel disease, stroke and cognitive decline and showed that smoking, oxidative stress and inflammation can cause vascular brain damage in COPD [221]. In the pcb-Cohort there

is a negative correlation between *APOE ε*4 carriers and respiratory disease. This deserves further clarification in other future studies.

Other notable risk factors are depression and APOE and these will be discussed in the following sections.

5.2 Depression

Depression affects modern populations and can be a heavy burden in the elderly. Thus, depression was addressed in the pcb-Cohort and will be discussed bearing in mind the following aspects:

- Evaluating depression and possible risk factors.
- Correlating depression with dementia in pcb-Cohort.

5.2.1 Depression in the pcb-Cohort and Possible Risk Factors

GDS15 is a validated tool to screen for, but not diagnose, possible cases of depression and adequate for use in primary care [155]. It is a quick application scale, with a yes/no response format. There is a validation study of the Portuguese version and this was applied [98,222]. The procedure involved applying the GDS15 but also evaluating how a previously published shorter version with only 4 questions (GDS4Lit) performed. The 568 patients in the pcb-Cohort were included in the data analysis. Of these 174 are classified as GDS15+. The number of the cases detect based in GDS4Lit is much higher (522) and did not prove to be a particularly useful tool in our hands, thus it will not be further discussed. Nonetheless shorter GDS versions (GDS4 to GDS8) were tested as described in the results.

Relative to sociodemographic factors associated with patients with depressive cases, the GDS15+ are mostly women, living alone, separated, retired or unemployed, low income and low literacy levels. These results are concordant with previous publications [221, 222]. Globally, the same parameters are equally relevant in the shorter versions, with the GDS4 showing a slight deviation (Table 23). In GDS15+ cases, relevant comorbidities are osteoarticular diseases, gastrointestinal tract and

dyslipidaemia (moderate significance). The short versions based on GDS15+ cases show the similar correlations (Table 24).

In literature, depression is associated with chronic somatic diseases [225]. Table 47 shows a literature review of the main comorbidities associating with depression. Mechanisms proposed for these associations are also briefly explained.

Table 47 Summary of comorbidities associating with depression

Comorbidity	Result
Cardiovascular disease	• Depression is exceedingly common in CVD patients and contributes to worse patient outcomes, including mortality, recurrent CVD events and health status [226]; • Mechanisms: Lifestyle (Smoking, Excessive alcohol use, Physical inactivity, Unhealthy diet, Lower treatment compliance and worse medical care); Pathophysiology: Metabolic deregulations, Immune-inflammatory deregulations, Autonomic deregulations, HPA-axis deregulations [227]; • Depression results in a 80–90% increased risk of cardiovascular disease [228]; • Depressed persons are at increased risk for peripheral atherosclerosis as indicated through e.g. coronary or aortic calcification, impaired endothelial function and increased arterial stiffness [229];
Gastrointestinal disease	• Anxiety, depression, panic attacks, posttraumatic stress disorders, and other somatization disorders are frequently detected prior to or simultaneously with the occurrence of functional gastrointestinal disorders [230]; • Depressive mood was significantly related to Functional Dyspepsia and Functional Dyspepsia + irritable bowel syndrome (IBS) overlap but not to IBS based on Rome III criteria. FD-IBS overlap patients have worse quality of life than FD-alone and IBS-alone patients [231]; • Anxiety is associated with uninvestigated and functional dyspepsia (Rome III criteria) in a Swedish population-based study [232];
Osteoarticular disease	• In the case of osteoarticular conditions, depression was associated with this somatic disease [225];
Diabetes Mellitus	• The prevalence of type 2 diabetes in major depression is 21.19%. Multivariate logistic regression analysis revealed that male gender, high blood pressure, Hypertriglyceridemia, Body Mass Index ≥30 kg/m², age ≥50 years, sleep duration <6.5 hours, C-reactive protein ≥4.5 mg/L, beck depression inventory >12, and apnea-hypopnea index ≥5/hour were significant risk factors of type 2 diabetes in major depression [233]; • Glycaemic control seem to influence the severity of depressive symptoms [146];
Dementia	• Depression is common in Alzheimer disease and other neuropathologies [234,235]; • MCI and dementia were associated with significantly higher rates of depression. Efforts to effectively engage and treat older adults with dementia will need also to address co-occurring depression [236]; • Depression being an independent risk factor in developing dementia [237,238]; • Depression affecting the threshold for manifesting dementia [238,239]; • Dementia or cognitive impairment being a feature of depression [238,240]; • The notion of depression being a prodromal of dementia [238,241]; • Depression being a reaction to cognitive decline [137,238]; • Dementia and depression sharing common risk factors explaining the increased prevalence of both in this population and why they are frequently comorbid [238,242]

Furthermore, to add further clinical relevance the DSM-5 for depression was not directly applied, as already explained, but rather patients with a diagnosis of confirmed depression (patients who were evaluated by psychiatry) were taken as true cases and designated as TrueDEP (74 cases, see Figure 11). Shorter versions of the GDS were likewise tested whereby the TrueDEP group was taken as the individuals with confirmed depression.

Relative to factors associated with the TrueDEP group, results are like those obtained using the GDS15+ group. Namely, gender, marital status, living arrangement, monthly family income and literacy, OA, GID and cognitive impairment appear to be risk factors. Likewise, the shorter GDS versions compared against the TrueDEP group revealed the same correlations. Thus, putatively validating the shorter versions. These will nonetheless have to be further validated.

Taken together the results for both the GDS15+ cases and TrueDEP groups are in agreement with the Portuguese study the Mental Health Report in Portugal [243]. This study shows that women present a greater risk than men of suffering from depressive disorders (OR=2.30) and anxiety disorders (OR=2.89), while men are more likely to suffer from disorders affecting the control of impulses and disturbances by substance abuse. Also in this study [243], the older group is less likely to suffer from depressive disorders, anxiety and substance abuse than younger age groups. The group of previously married (separated/divorced/widowed) persons is at a higher risk of suffering from depressive disorders and substance abuse, whereas those who have never been married are associated with a greater risk of substance abuse and impulse control disorders. Regarding the influence of the level of education, there is an association between the medium-low level and the disorders of impulse control and substance abuse disorders. The level of income, as estimated in the study, does not show significant associations with the variables of psychiatric morbidity. Overall conclusions are like those obtained for the pcb-Cohort.

5.2.2 Correlating Depression and Dementia

Depression and dementia are common in older individuals and their association is very complex, further, the coexistence of both has emerged as a significant public health problem leading to increased health care utilization and costs [173]. The question 'Are depressed people also in an early stage of dementia?' is of some concern. Depression has been described to be a risk factor for dementia [152]. It is a condition that reduces the quality of life for the patients [244]. Demented patients can also exhibit a depressed state [138,209]

In the pcb-Cohort, the number of patients with both conditions is striking (Table 48). Specifically, 87 and 36 patients with suspected cognitive disorder, based on the CDR evaluation are GDS15+. Comparatively in the TrueDEP equivalent numbers fall to 37 and 15 for CDR=0.5 and CDR>=1 respectively. Reports in the literature, indicate that rates of depression are significantly higher in subjects with MCI and dementia when compared to those with normal cognition [236].

Table 48 Correlating patients with GDS results and cognitive evaluation

Cognitive Evaluation		GDS		Depressive case		
		GDS15-	GDS15+	Normal	TrueDEP	Inconclusive
CDR	CDR=0	250	51	189	22	90
	CDR=0.5	112	87	76	37	86
	CDR>=1	32	36	21	15	32
Total		394	174	286	74	208
NCD	NCD=0	189	0	189	0	0
	NCD-mild	61	0	61	0	0
	NCD-major	36	0	36	0	0
	PCD	108	174	0	74	208
Total		394	174	286	74	208

Abbreviations: GDS-Geriatric Depression Scale; (-) negative cases; (+) positive cases; TrueDEP: confirmed cases of depressive disorder bases in DSM-5; Inconclusive-cases that not conclude the diagnostic of depressive disorder; CDR-Clinical Dementia Rate; NCD-Neurocognitive disorder; PCD-Possible cases of depression; N total= 568 patients in pcb-Cohort

Consistently in the pcb-Cohort, dementia and depressive conditions show an association (Tables 25 and 34). Not surprisingly depressive symptoms have in the past been correlated to neuropsychological variables, MMSE, cognitive profiles, daily life activities and age of onset [135].

5.3 *APOE* Genotyping in pcb-Cohort

The APOE genotype is an important determinant of the risk of dementia [192,245], AD and depression [200]. Apolipoprotein E has three alleles:ε2/ε3/ε4 [199], where epsilon4 is the major genetic risk factor for AD [245]. In the pcb-Cohort,ε3ε3 (75%) was the most common polymorphism, andε2ε4 (1.4%) was the rarest. Theε2ε4 genotyping is represented in 1.4%. There was noε2ε2 individual [201], (Figure 13). Carriers of ε4 represent 96 in 508 (18.9%) patients in pcb-Cohort.

Relative to sociodemographic characteristics associating with *APOE ε*4, no significant associations between *APOE ε*4 allele and gender was found in the pcb-Cohort. The proportion of patients with dementia carrying the ε4 allele was estimated to be 20%, but at a population level, it must be born in mind that factors other than the *APOE* genotype play an important role in dementia onset [193]. The risk *APOE ε*4 association with dementia has been shown in developed countries and in Asia, but not in Africa or in Latin America [89]. In the pcb-Cohortε4 also appears to be a risk factor (Tables 13 and 18) with respect to CDR≥1 and NCD-mild, curiously no such relationship was found for NCD-major; due to the exclusion of patients with depression. In fact, there are reports showing a correlation between depression and *APOE ε*4 allele [199,200]. In pcb-Cohort, this correlation is also found; GDS15+ cases are in higher proportion inε4carriers (p-value=0.041).

Furthermore, *APOE ε*4 has been related to other disorders. In fact *APOE ε*4 has been reported to associate with increased cardiovascular risk [200,246] and dyslipidaemia [246]. In the pcb-Cohort a correlation between *APOE ε*4 carriers and dyslipidaemia is evident (Table 37). It is also worthwhile noting that a high risk *APOE ε*4 genotype can be counterbalanced by high-density lipoproteins (HDL) [246].

Additionally, data from the pcb-Cohort revealed a higher prevalence of chronic respiratory diseases in non-ε4 carriers. The mechanism by which *APOE ε*4 non-carrier´s contribute to the pathogenesis of respiratory disease remains to be elucidated.

Relative to *APOE ε2* carriers, this allele has been associated to a protective role to cognitive impairment [193]. In the pcb-Cohort, theε2 carriers and prevalence appears to increase in the age range of 50-64 years. Relative to NCD evaluation, no

correlation with this allele was found (Table 37). But it is possible to see that the proportion of the normal cognitive performance is marginally higher in *APOE* ε2 carriers (73.7% vs 62.1% non ε2 carrier).

Dyslipidaemia, cardiac and vascular disease and Type 2 diabetes are tightly linked. *APOE* ε2 carriers in the pcb-Cohort show a negative association with both dyslipidaemia (p-value=0.009) and cardiac and vascular disease (p-value=0.053). Further, in the pcb-Cohort, it is possible to see that DM is in a higher proportion in *APOE* ε2 non-carrier (20.6% vs 7.9% of *APOE ε2* carrier, p-value=0.057). Other reports have shown that in healthy patients, *APOE ε2* carriers are associated with reduced cardiovascular disease [199], and that Type 2 diabetes individuals have increased risk of developing AD [195]. So, in a primary care setting the screening and control of the above-mentioned three pathologies may aid in dementia prevention.

5.4 Considerations when Working in Primary Health Care Settings

Considering the limited access to specialized health care that particularly affects the elderly, primary care providers are usually on the front line in the diagnosis and care of these patients [247]. Depression is common across the population, and imposes social, financial, and medical costs to patients and their families [248]. Screening for depression can be useful in the primary care setting if reliable systems are in place to ensure adequate treatment and follow-up [248]. Use of collaborative care models for depression in the primary care setting have been shown to be a cost-effective means of providing depression-related care, but economic and cultural barriers continue to slow down widespread acceptance [248]. The fact that older adults seek treatment for depression in primary care settings led to the development of collaborative care interventions for depression. These interventions have consistently demonstrated clinically meaningful effectiveness in the treatment of late-life depression [158].

Relative to dementia, this pathology still does not have the same evolution in primary health care as hypertension, diabetes and diseases of the cardiovascular system. It is fact that the training, the dedication in weekly working hours is greater for the latter pathologies. There is perhaps a deficit in recognizing dementia ([110]. In

practice, this means that there is perhaps a lower dementia recognition rate, and it would be important for potential cases to be identified as early as possible and referred to a specialist (neurologist or psychiatrist). As with other pathologies, the family doctor does not substitute other specialists, but they complement each other. The norms of the General Directorate of Health (Direção-Geral da Saúde) already have guidelines for diagnosis and therapy of many pathologies like DM and HYP [249]. Currently the family doctor suspects, applies a quick test and recommends the patient to specialized consultations. It would be important to include dementia in this workflow.

In the above-suggested scenario, brief cognitive tests could be implemented for the identification of cognitive deficits at the community and primary health care levels. In addition, these tests are useful in monitoring the progression of cognitive deficits and evaluating the efficacy of anti-dementia drugs or other intervention strategies. There are several short cognitive assessment tests, but only a few are adapted for use in Portugal [98]. The Mini-Mental State Examination (MMSE) is a good tool for detecting dementia, but it is not usually altered in the early stages of cognitive decline, such as a mild cognitive defect [112]. Several other instruments have been proposed to detect early stages of cognitive decline. The Montreal Cognitive Assessment (MOCA) test [250] has recently been translated, adapted and validated for Portugal [251] and can be recommended. The MOCA shows sensitivity values of 84% and specificity of 79% for detection of mild cognitive impairment, and sensitivity values of 77% and specificity of 80% for detection of Alzheimer's disease [252].

In the pcb-Cohort the use of a quick test the MMSE was employed but also the ‘gold standard’ CDR. This permitted comparing a more complete test with one that is quicker to employ. However given that the CDR is more complete than the MMSE, it was chosen to be used primarily in this study, furthermore it has already been validated in the Portuguese version [253]. It has also been shown to be a very effective tool in evaluating various forms of dementia [254] and has cross-cultural validity [112,183,233].

Previous studies have shown that the CDR has a diagnostic accuracy of 96% in patients with mild cognitive disturbance, 97.1% in patients with AD and a CDR≥0.5 and

an accuracy of 87.2% in AD patients with a CDR≥1 [98]. Clearly attention should be given to patients with CDR=0.5. This is a heterogeneous group where CDR=0.5 incorporates several conditions: questionable dementia, incipient or very mild dementia and still Alzheimer's type dementia [135,234]. Therefore, in the results from the first part of the thesis, patients with CDR=0.5 represent in fact this heterogeneous group, which needs to be re-evaluated later to better define the group.

Another methodology that could have been used is the sum of the scores obtained in each category (or box), with an amplitude of 0 to 18, in which the highest scores correspond to the greatest severity [105,183]. It also has validity in clinical practice and research. We chose not to use it once we detected people with a score of 0.5 and who had changes in orientation for example, not memory, and that did not match the overall score.

In this phase of the study, we have not yet been able to completely re-evaluate the pcb-cohort. Thus, we have an idea of cognitive deficit prevalence but not incidence. A re-evaluation is ongoing, and the results should be forthcoming. In the future it will be interesting to identify how many new confirmed cases occurred, what therapy was used, and the impact of starting treatment on the evolutionary performance of dementia in our region. This is feasible because the individuals' data obtained for each patient during the study here presented was made available to the respective family doctor.

This thesis has the advantage of being a study with the purpose of recommending an effective protocol of joint action involving general practitioners (GP), psychiatrists and neurologists, among others. Like other comorbidities, dementia and depression have to be seen as a public health problem in Portugal, and in the world [25]. People living with dementia have poor access to appropriate healthcare, even in most high-income countries, where only around 50% of people living with dementia receive a diagnosis. In low and middle-income countries, less than 10% of cases are diagnosed. As the populations age, due to increasing life expectancy, the number of people with dementia is increasing [25]. The recommendation of a good proposal to identify cases of dementia, would include players already involved, for example between the referral hospital and primary health care centres, such as the maternal health protocol presently in action. The contribution of this thesis lies in that

it was able to profile cognitive impairment and depression in primary health care settings. It was also able to determine the main factors associated with dementia and depression and these are largely consistent accepted hypotheses. One of the strengths of this study is that it presents a set of internationally validated tools that can be employed and appear to do well in primary care settings. Further validations can of course be considered. Similar studies have already been carried out in other countries [63].

5.5 Polypharmacy and Potentially Inappropriate Medication in the pcb-Cohort

The elderly population is at risk of polypharmacy and Potentially Inappropriate Medication Use (PIM). Polypharmacy is a problem because individuals over 65 years old often have to deal with multiple illnesses [256]. The Beers Criteria is a guide to improve medical prescription [257]. Further interest arises in its use as a tool in primary care settings [258]. The aim of this part of the work was to identify and analyse polypharmacy and PIM in the pcb-Cohort.

As mentioned, in the elderly, the increase in medication is particularly due to co-morbidities arising with ageing. Another important feature are the physiological changes: pharmacokinetics and pharmacodynamics, these are all important because what is observed is increased susceptibility to polypharmacy, drug interactions, adverse drug reactions, prescribing cascade, poor compliance, and potential inappropriate prescribing [175] .

In the pcb-Cohort 366 participants are 65 years old or older and medication information was available for 361. Results show that the average number medications taken by individuals in the pcb-Cohort is in the range of that found in other studies. In Austria, the average number of different drugs prescribed per person was 9.0, (7.9 in men and 9.7 in women) [259]. In Ireland, the average number of different medications per patient was 5 (range 1–19) [260]. In the pcb-Cohort the average number medications is 5 in men and 7 in women. However, polypharmacy prevalence in the pcb-Cohort is strikingly high; 94.5% of the 361 individuals are subject to polypharmacy.

Multivariate analyses, using logistic regression, revealed the factors that significantly contribute to increased risk of polypharmacy; 1.9 times greater in patients over 75; 2.6 times in patients with low average of schooling; 2 times in patients with CVD, and the risk for the presence of PIM1 increases 4.6 times in the same patient group (Table 45).

The presence of polypharmacy itself does not denote inappropriate or incorrect use of medications. Older adults with more than one chronic medical condition typically require polypharmacy to manage their conditions [261]. Patients who take multiple medications are at higher risk of experiencing medication-related problems [164]. Another problem is that there is an economic burden caused by polypharmacy because older adults who live on a fixed income often have difficulty affording their medications [261]. In the literature, positive associations of neurological motor dysfunction, older age, cognitive impairment, disability in activities of daily living were associated with polypharmacy [256].

The Beers Criteria is a tool with great relevance in European countries [166]. It is known that applying the Beers Criteria can decrease by 0.5 the number of medications in patients admitted to acute geriatric centres [262]. Relative to PIM1, we found that 47.4% of individuals in the pcb-Cohort use at least one PIM medication (Table 49). This is strikingly high compared to studies showing a much lower prevalence of inappropriate medication usage in Europe and in the United States [263,264]. A study in Finland estimated the prevalence rate of inappropriate prescribing to be 12.5%, 1.3%, and 0.2% for individuals taking at least 1, 2, or 3 inappropriate PIM1 drugs, respectively [263]. For the pcb-Cohort individuals taking at least 1, 2, 3 or 4 inappropriate PIM1 drugs show a prevalence of 29.6%, 14.7%, 2.5% and 0.6% respectively.

In the pcb-Cohort, the more frequent PIM1 medications are Benzodiazepines: with 44.1% of the prescriptions falling into PIM1 (Table 49). The prescription of this medication is inappropriate because of the extended sedation and increased risk of falls [265]. Benzodiazepines are also associated with cognitive problems and represent an increased risk of developing dementia [266,267]. There are reports that Benzodiazepines were prescribed for approximately one in three elderly hospitalized

patients and that a large proportion was inappropriate [268]. Also, commonly prescribed Beers Criteria drugs used in dentistry include Benzodiazepines and long-acting non-steroidal anti-inflammatory analgesics [269].

Table 49 Comparative PIM prevalence

REF	Country	PIM Prevalence	Main PIMs
pcb-Cohort	Aveiro, Portugal	47.4%	Benzodiazepines (44.1%), vasodilators (25.5%), drugs with antimuscarinic properties (16.7%), benzodiazepines long-acting (8.6%).
[269]	USA (dentistry)	3 in 10 older adults visiting the dentist	Benzodiazepines long-acting and/or nonsteroidal anti-inflammatory analgesics.
[270]	France	53.6% in patients ≥ 75 years old	Vasodilators (19.4%), drugs with antimuscarinic properties (19.3%), benzodiazepines long-acting (17.8%).
[271]	France	geriatric teaching hospital 26.7%	24% of these patients with PIM1 use at the time of hospital admission, namely psychotropics.
[272]	Taiwan	metropolitan hospital (14.4%) academic medical centres (11.1%)	Antihistamines (4.8% of all prescriptions in 48.3% of elderly patients), muscle relaxants/antispasmodics (4.0% and 40.3%, respectively), long-acting benzodiazepines (2.4% and 21.4%).

Beyond the above-mentioned PIM1 drugs, another important group of drugs in this group are the antipsychotics. In the pcb-Cohort there is a frequency of 4.4% PIM1 due to antipsychotic drugs. Antipsychotics are associated with restlessness which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated (akathisia) [273]. Antipsychotics are associated with worsening Parkinsonism as psychosis and dementia are frequently comorbidities in patients with Parkinson's Disease (PD). Safety risks associated with antipsychotics mean that this class of drugs should be used with precaution [274].

Also, of concern is the use of aspirin, which is typically used for primary prevention of cardiac events, it should nonetheless be used with caution in adult's ≥80 years old. Aspirin can cause bleeding of the gastrointestinal tract followed iron deficiency anaemia, in fact there is a lack of evidence in what regards benefit versus risk in aspirin usage in individuals ≥80 years old [166,275]. In the pcb-Cohort 12 (17.6%) of 86 patients, aged 80 years old use Aspirin.

Of equal interest in the pcb-Cohort, are the 4 patients diagnosed with chronic Kidney disease, of which 1 is taking NSAIDs. In chronic kidney disease, stages IV and V NSAIDs should be avoided because they may increase the risk for kidney Injury [166]. Although only one patient is in this situation it is nonetheless undesirable. NSAIDs in the elderly are effective for the treatment of Musculoskeletal diseases although the risk of serious adverse events (mainly gastrointestinal) is also clearly high [276]. Vasodilators should also be avoided in patients over 65 years [166], since they are an important cause of Syncope in this age group [277]. In our study, 94 (24.7%) patients were taking a vasodilator. Fortunately, there are no cases of Syncope in these patients.

Multivariate analyses, using logistic regression, permitted identifying the factors that significantly contribute to increasing the risk of PIM1 (Table 42). Regarding the risk of PIM1, attention should be given to women with 1.3 times increased risk and the group with cognitive impairment (NCD) with an increased risk of 2.6 times. Regarding patients with polypharmacy, these are 4.6 times more likely to take PIM1. In literature, positive associations with PIM1 were found with recent hospitalization, number of prescriptions, and comorbidity including circulatory diseases, endocrine and metabolic disorders [166,269,271].

Beers criteria goes beyond a list of medications, it is a guide for good medical practice. It assists with determining when a drug should or should not be used, although individual situations should always be considered.

For example: the use of amitriptyline (an anti-depressive) is not as a first drug of choice for depression but can be used for neuropathic pain given its secondary benefits. In fact, a good command of clinical pharmacology is absolutely necessary for a correctly prescribing medications and the Beers criteria can strongly assist [257,262,278]. But the Beers Criteria are not perfect, not all inappropriate medications are considered. The other flaw is that these criteria do not over adverse drug reactions [279,280].

In closing, the Beers criteria are not the only tool for assisting with drug prescribing. There are other tools, such as the START/STOP tool [262]. The pcb-Cohort was not designed with tools to apply the latter. However, the possibility of evaluating medication and STOP / START application and subsequent comparison with our results

of the Beers criteria presented here is not completely ruled out. In follow, up work we aim to raise awareness among primary care colleagues so that they apply the Beers criteria and then evaluate the effectiveness of this intervention. Namely to monitor the medications inappropriately prescribed.

5.6 Limitations

This study focussed on dementia and depression thus some important characteristics were not collected, like smoking and obesity, also imaging data or neurochemical CSF analyses were not available; some questions necessary to apply DSM-5 criteria to depressive disorder were not included; and details regarding cardiovascular risk. Some of this information would have been useful to carry out further association studies.

Another important consideration is that the study group was collected from primary health care centres and thus best reflects the patients attending these types facilities. Finally, several shorter tests were proposed for putative depression, for example the GDS4-8, for wider usage further validation studies should be carried out.

CHAPTER 6

Closing Remarks

This study shows the merit of carrying out cognitive tests on younger subjects; in the age group of 50–65 years, 71 individuals were identified as possibly demented or demented. One may conclude that for the pcb-Cohort, the *APOE ε4* allele, female gender, ageing, and low education are risk factors. The most unexpected finding was a strong correlation between GID and high CDR scores. This hitherto unreported correlation deserves further investigation. It is expected that the methodology used in the pcb-Cohort may serve as an effective tool to identify possible markers and risk factors for similar studies and as such may contribute to dementia diagnosis in a primary care setting.

This study presents a set of validated tools that can be employed in a primary care setting to identify potential dementia cases. Ageing is a known risk factor for dementia; however, in the pcb-Cohort, age group subdivisions allowed for the identification of potential dementia cases among younger volunteers. This is important, since it can endorse cognitive testing of younger patients in a primary care setting. In fact, a major strength of the pcb-Cohort study is that it identified 64 subjects with suspected dementia and 7 with mild dementia; these individuals were flagged for follow-up studies. Additionally, considering the available comorbidity data, GID appears to be a risk factor; this should be considered in future studies.

Relative to depression, GDS4Lit is not an adequate tool for screening for depression in Portuguese patients in the pcb-Cohort. Our results show that GDS8 is a simple tool compatible with primary care clinicians and capable of identifying high-risk older patients who could be targeted for subsequent depression screening. Restricting depression screening to patients identified as high risk by the GDS8 may enable clinicians to maximize the potential benefits of screening while minimizing possible harms. Therefore, we recommend that in usual practice the GDS8 be applied and followed up when justifiable by a formal diagnostic procedure to establish the presence depression.

The work here presented is to our knowledge the first genotyping APOE study in the Aveiro region of Portugal. In this region, the main genotyping isε3ε3 andε4 carriers are potential cases of dementia and depression.

Relative to medication, in the pcb-Cohort there is a high prevalence of PIM and polypharmacy among primary care patients over 65. Using the Beers criteria is a helpful guide and a good screening tool to detect PI prescription. We therefore recommend its use at the point of care.

Future studies in the pcb-Cohort will focus on reassessing patients; evaluating the progression of dementia in the region of Aveiro; study the presence and/or evolution of comorbidities; apply the STOP / START criteria and compare with Beers Criteria and conduct primary health care training and support as requested in the health community.

References

[1] Maria José Carrilho. Revista de Estudos Demográficos. Rev Estud Demográficos 2014;54.

[2] Instituto Nacional de Estatística. XV recenciamento geral da população. CENSOS 2011 2016.

[3] Alda de Caetano Carvalho. Estatísticas Demográficas 2013. 73rd ed. Lisboa: 2013.

[4] Explained eurostat statistic. Population structure and ageing 2016.

[5] Navaratnarajah A, Jackson SHD. The physiology of ageing. Medicine (Baltimore) 2013;41:5–8. doi:10.1016/j.mpmed.2012.10.009.

[6] Newton JL. Changes in upper gastrointestinal physiology with age. Mech Ageing Dev 2004;125:867–70. doi:10.1016/j.mad.2004.05.007.

[7] Maguire SL, Slater BMJ. Physiology of ageing. Anaesth Intensive Care Med 2013;14:310–2. doi:10.1016/j.mpaic.2013.04.008.

[8] Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol 2014;117:20–40. doi:10.1016/j.pneurobio.2014.02.004.

[9] Fontana L. Modulating human aging and age-associated diseases. Biochim Biophys Acta - Gen Subj 2009;1790:1133–8. doi:10.1016/j.bbagen.2009.02.002.

[10] Prince M, Wimo A, Guerchet M, Gemma-Claire A, Wu Y-T, Prina M. World Alzheimer Report 2015: The Global Impact of Dementia - An analysis of prevalence, incidence, cost And trends 2015:84. doi:10.1111/j.0963-7214.2004.00293.x.

[11] Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimer's Dement 2015;11:332–84. doi:10.1016/j.jalz.2015.02.003.

[12] World Health Organization. World Health Statistics 2017: Monitoring Health for The Sustainable Development Goals. 2017. doi:10.1017/CBO9781107415324.004.

[13] Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006;113:791–8. doi:10.1161/CIRCULATIONAHA.105.548206.

[14] Who. 100 Core Health Indicators 2015:1–136. doi:WHO/HIS/HSI/2015.3.

[15] Hanahan D, Weinberg R a. Hallmarks of cancer: The next generation. Cell 2011;144:646–74. doi:10.1016/j.cell.2011.02.013.

[16] Hanahan D, Weinberg R a, Francisco S. The Hallmarks of Cancer Review University of California at San Francisco 2000;100:57–70.

[17] Heilbronn LK, Ravussin E. Calorie restriction and aging: review of the literature and implications for studies in humans. Am J Clin Nutr 2003;78:361–9.

[18] Everitt A, Rattan S, Couteur D, de Cabo R. Calorie Restriction, Aging and Longevity. Springer; 2010.

[19] Omodei D, Fontana L. Calorie restriction and prevention of age-associated chronic disease. FEBS Lett 2011;585:1537–42. doi:10.1016/j.febslet.2011.03.015.

[20] Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci 2010;31:89–98. doi:10.1016/j.tips.2009.11.004.

[21] Anderson RM, Weindruch R. Metabolic reprogramming, caloric restriction and aging. Trends Endocrinol Metab 2010;21:134–41. doi:10.1016/j.tem.2009.11.005.

[22] Pancani T, Anderson KL, Brewer LD, Kadish I, DeMoll C, Landfield PW, et al. Effect of high-fat diet on metabolic indices, cognition, and neuronal physiology in aging F344 rats. Neurobiol Aging 2013;34:1977–87. doi:10.1016/j.neurobiolaging.2013.02.019.

[23] Walhovd KB, Storsve AB, Westlye LT, Drevon C a, Fjell AM. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. Neurobiol Aging 2014;35:1055–64. doi:10.1016/j.neurobiolaging.2013.11.011.

[24] PSD. PROJECTO DE RESOLUÇÃO N.o 287/XI/2.a 2010:1–7.

[25] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer Report 2016 Improving healthcare for people living with dementia. Coverage, Quality and costs now and in the future. Alzheimer's Dis Int 2016:1–140.

[26] The prevalence of dementia in Europe -Portugal 2014. http://www.alzheimer-europe.org/Policy-in-Practice2/Country-comparisons/2013-The-prevalence-of-dementia-in-Europe/Portugal (accessed November 20, 2017).

[27] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013;9:63–75.e2. doi:10.1016/j.jalz.2012.11.007.

[28] Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of Dementias and Alzheimer's Disease. Arch Med Res 2012;43:600–8. doi:10.1016/j.arcmed.2012.11.003.

[29] Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, et al. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med 2005;352:2515–23. doi:10.1056/NEJMsa043266.

[30] Kester MI, Scheltens P. Dementia 2009:241–51. doi:10.1136/jnnp.2009.182477.

[31] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. 2013.

[32] Berger G, Bernhardt T, Weimer E, Peters J, Kratzsch T, Frolich L. Longitudinal study on the relationship between symptomatology of dementia and levels of subjective burden and depression among family caregivers in memory clinic patients. J Geriatr Psychiatry Neurol 2005;18:119–28. doi:10.1177/0891988704273375.

[33] Tartaglia MC, Rosen HJ, Miller BL. Neuroimaging in dementia. Neurotherapeutics 2011;8:82–92. doi:10.1007/s13311-010-0012-2.

[34] Winblad I, Viramo P, Remes a., Manninen M, Jokelainen J. Prevalence of dementia - A rising challenge among ageing populations. Eur Geriatr Med 2010;1:330–3. doi:10.1016/j.eurger.2010.10.002.

[35] Robillard A. Clinical diagnosis of dementia. Alzheimers Dement 2007;3:292–8. doi:10.1016/j.jalz.2007.08.002.

[36] Association AP. DSM 5. 2013. doi:10.1176/appi.books.9780890425596.744053.

[37] Birgegard A, Norring C, Clinton D. DSM-IV versus DSM-5: Implementation of proposed DSM-5 criteria in a large naturalistic database. Int J Eat Disord 2012;45:353–61. doi:10.1002/eat.20968.

[38] Perneczky R, Alexopoulos P, Kurz a. Mild cognitive impairment. MMW Fortschr Med 2004;146:34–7. doi:http://dx.doi.org/10.1212/01.CON.0000429175.29601.97.

[39] Hänninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. Acta Neurol Scand 2002;106:148–54. doi:10.1034/j.1600-0404.2002.01225.x.

[40] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL. Practice parameter : Early detection of dementia : Mild cognitive impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology DeKosky This information is current as of November 22 , 2009 The o. Neurology 2009;56:1133–42.

[41] Kelley BJ, Petersen RC. Alzheimer's Disease and Mild Cognitive Impairment. Neurol Clin 2007;25:577–609. doi:10.1016/j.ncl.2007.03.008.

[42] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8. doi:10.1001/archneur.56.3.303.

[43] Chertkow H, Nasreddine Z, Joanette Y, Drolet V, Kirk J, Massoud F, et al. Mild cognitive impairment and cognitive impairment, no dementia: Part A, concept and diagnosis. Alzheimers Dement 2007;3:266–82. doi:10.1016/j.jalz.2007.07.013.

[44] Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ, et al. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol 2003;62:1087–95.

[45] Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. Neurology 2005;64:834–41. doi:10.1212/01.WNL.0000152982.47274.9E.

[46] Davis KL, Mohs RC, Marin D, Purohit DP, Perl DP, Lantz M, et al. Cholinergic markers in elderly patients with early signs of Alzheimer disease. JAMA 1999;281:1401–6. doi:10.1001/jama.281.15.1401.

[47] Galvin JE. Dementia with Lewy bodies. Arch Neurol 2003;60:1332–5. doi:10.1001/archneur.60.9.1332.

[48] Thompson S a., Lennox G. Inflammatory and infective causes of dementia. Psychiatry 2008;7:29–32. doi:10.1016/j.mppsy.2007.11.007.

[49] Dennis MS. Other causes of dementia. Psychiatry 2008;7:33–5. doi:10.1016/j.mppsy.2007.11.011.

[50] Gooblar J, Carpenter BD, Coats M a., Morris JC, Snider BJ. The influence of cerebrospinal fluid (CSF) biomarkers on clinical dementia evaluations. Alzheimer's Dement 2014;11:533–540.e2. doi:10.1016/j.jalz.2014.04.517.

[51] Duits FH, Prins ND, Lemstra AW, Pijnenburg Y a L, Bouwman FH, Teunissen CE, et al. Diagnostic impact of CSF biomarkers for Alzheimer's disease in a tertiary memory clinic. Alzheimer's Dement 2014;11:523–32. doi:10.1016/j.jalz.2014.05.1753.

[52] Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, Jeromin A, et al. The future of blood-based biomarkers for Alzheimer's disease. Alzheimer's Dement 2014;10:115–31. doi:10.1016/j.jalz.2013.01.013.

[53] Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: Clinical features, diagnosis, and management. Front Neurol 2012;MAY:1–15. doi:10.3389/fneur.2012.00088.

[54] Aluise CD, Sowell R a, Butterfield DA. Peptides and proteins in plasma and cerebrospinal fluid as biomarkers for the prediction, diagnosis, and monitoring of therapeutic efficacy of Alzheimer's disease. Biochim Biophys Acta 2008;1782:549–58. doi:10.1016/j.bbadis.2008.07.008.

[55] Gandy S. Molecular basis for anti-amyloid therapy in the prevention and treatment of

Alzheimer's disease. Neurobiol Aging 2002;23:1009–16.

[56] Da Cruz E Silva OAB, Rebelo S, Vieira SI, Gandy S, Da Cruz E Silva EF, Greengard P. Enhanced generation of Alzheimer's amyloid-?? following chronic exposure to phorbol ester correlates with differential effects on alpha and epsilon isozymes of protein kinase C. J Neurochem 2009;108:319–30. doi:10.1111/j.1471-4159.2008.05770.x.

[57] Da Cruz e Silva EF, Da Cruz e Silva OAB. Protein phosphorylation and APP metabolism. Neurochem Res 2003;28:1553–61. doi:10.1023/A:1025630627319.

[58] Song F, Poljak A, Smythe G a., Sachdev P. Plasma biomarkers for mild cognitive impairment and Alzheimer's disease. Brain Res Rev 2009;61:69–80. doi:10.1016/j.brainresrev.2009.05.003.

[59] Trojanowski JQ, Vandeerstichele H, Korecka M, Clark CM, Aisen PS, Petersen RC, et al. Update on the biomarker core of the Alzheimer's Disease Neuroimaging Initiative subjects. Alzheimer's Dement 2010;6:230–8. doi:10.1016/j.jalz.2010.03.008.

[60] Buerger K, Frisoni G, Uspenskaya O, Ewers M, Zetterberg H, Geroldi C, et al. Validation of Alzheimer's disease CSF and plasma biological markers: The multicentre reliability study of the pilot European Alzheimer's Disease Neuroimaging Initiative (E-ADNI). Exp Gerontol 2009;44:579–85. doi:10.1016/j.exger.2009.06.003.

[61] Prince M, Jackson J. World Alzheimer Report 2009. Alzheimer's Dis Int 2009:1–96.

[62] Pender R. World Alzheimer Report 2014 Dementia and Risk Reduction 2014:104.

[63] Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: A systematic review with meta-analyses and qualitative analyses. PLoS One 2012;7. doi:10.1371/journal.pone.0038268.

[64] Cummings JL. Alzheimer's Disease 2004:56–67.

[65] Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant E a, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol 2013;12:957–65. doi:10.1016/S1474-4422(13)70194-7.

[66] Forlenza O V., Diniz BS, Talib LL, Radanovic M, Yassuda MS, Ojopi EB, et al. Clinical and biological predictors of Alzheimer's disease in patients with amnestic mild cognitive impairment. Rev Bras Psiquiatr 2010;32:216–22. doi:10.1590/S1516-44462010005000002.

[67] Oliveira J, Soares M, Almeida C De, Odete AB, Henriques AG. Protein Phosphorylation is a Key Mechanism in Alzheimer ' s Disease 2017;58:953–78. doi:10.3233/JAD-170176.

[68] Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143–53. doi:10.1212/WNL.56.9.1143.

[69] Holmes C. Dementia. Medicine (Baltimore) 2012;40:628–31. doi:10.1016/j.mpmed.2012.08.012.

[70] Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. Exp Neurol 2015. doi:10.1016/j.expneurol.2015.05.006.

[71] Shimomura T. Dementia with Lewy bodies. Nippon Rinsho Japanese J Clin Med 2004;62 Suppl:122–6. doi:10.4324/9780203829653.

[72] Cromarty R a., Elder GJ, Graziadio S, Baker M, Bonanni L, Onofrj M, et al. Neurophysiological biomarkers for Lewy body dementias. Clin Neurophysiol 2015. doi:10.1016/j.clinph.2015.06.020.

[73] McGinnis SM. Neuroimaging in neurodegenerative dementias. Semin Neurol 2012;32:347–60. doi:10.1055/s-0032-1331808.

[74] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology 2005;65:1863–72. doi:10.1212/01.wnl.0000187889.17253.b1.

[75] Vintém APB, Henriques AG, da Cruz e Silva OAB, da Cruz e Silva EF. PP1 inhibition by Aβ peptide as a potential pathological mechanism in Alzheimer's disease. Neurotoxicol Teratol 2009;31:85–8. doi:10.1016/j.ntt.2008.11.001.

[76] Roberson ED. Frontotemporal dementia. Curr Neurol Neurosci Rep 2006;6:481–9. doi:10.1007/s11910-006-0050-7.

[77] Rosen HJ, Lengenfelder J, Miller B. Frontotemporal dementia. Neurol Clin 2000;18:979–92. doi:10.1016/S0733-8619(05)70235-8.

[78] Gorno-Tempini ML, Hillis a. E, Weintraub S, Kertesz a., Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–14. doi:10.1212/WNL.0b013e31821103e6.

[79] Massano J. Clinical, genetic and neuropathological features of frontotemporal dementia: An update and guide . Acta Medica Port 2013;26:392–401.

[80] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 2011;134:2456–77. doi:10.1093/brain/awr179.

[81] Martinez P, Sophia R. Cognitive impairment and dementia in Parkinson ' s disease : clinical features , diagnosis , and management 2012;3:1–15. doi:10.3389/fneur.2012.00088.

[82] Roussotte FF, Gutman B a, Madsen SK, Colby JB, Narr KL, Thompson PM. The apolipoprotein E epsilon 4 allele is associated with ventricular expansion rate and surface morphology in dementia and normal aging. Neurobiol Aging 2014;35:1309–17. doi:10.1016/j.neurobiolaging.2013.11.030.

[83] Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. Prog Neurobiol 2014. doi:10.1016/j.pneurobio.2014.02.004.

[84] Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott a., Amaducci L a., et al. Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. Neurology 1999;52:78–78. doi:10.1212/WNL.52.1.78.

[85] Fillenbaum GG, Heyman A, Huber MS, Woodbury MA, Leiss J, Schmader KE, et al. The prevalence and 3-year incidence of dementia in older Black and White community residents. J Clin Epidemiol 1998;51:587–95. doi:10.1016/S0895-4356(98)00024-9.

[86] Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991;349:704–6. doi:10.1038/349704a0.

[87] van Duijn CM. Epidemiology of the dementias: recent developments and new approaches. J Neurol Neurosurg Psychiatry 1996;60:478–88.

[88] Patterson C, Feightner JW, Garcia A, Hsiung G-YR, MacKnight C, Sadovnick AD. Diagnosis and treatment of dementia: 1. Risk assessment and primary prevention of Alzheimer disease. vol. 178. 2008. doi:10.1503/cmaj.070796.

[89] Guerreiro RJ, Baquero M, Blesa R, Boada M, Brás JM, Bullido MJ, et al. Genetic

screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol Aging 2010;31:725–31. doi:10.1016/j.neurobiolaging.2008.06.012.

[90] Bird TD. Genetic Factors in Alzheimer ' s Disease 2005:862–4.

[91] Bettens K, Sleegers K, Van Broeckhoven C. Genetic insights in Alzheimer's disease. Lancet Neurol 2013;12:92–104. doi:10.1016/S1474-4422(12)70259-4.

[92] Solé-Padullés C, Bartrés-Faz D, Junqué C, Vendrell P, Rami L, Clemente IC, et al. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 2009;30:1114–24. doi:10.1016/j.neurobiolaging.2007.10.008.

[93] Stern Y. Cognitive reserve. Neuropsychologia 2009;47:2015–28. doi:10.1016/j.neuropsychologia.2009.03.004.

[94] Ai AL, Pappas C, Simonsen E. Risk and Protective Factors for Three Major Mental Health Problems Among Latino American Men Nationwide. Am J Mens Health 2014. doi:10.1177/1557988314528533.

[95] Farrer L a, Cupples LA, Haines JL, Hyman B, Kukull W a, Mayeux R, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease. JAMA J Am Med Assoc 1997;278:1349–56. doi:10.1001/jama.1997.03550160069041.

[96] Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry 1998;55:809–15. doi:http://dx.doi.org/10.1001/archpsyc.55.9.809.

[97] Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the cognitive function and ageing study i and II. Lancet 2013;382:1405–12. doi:10.1016/S0140-6736(13)61570-6.

[98] M. R. Simões IS e G de E de EC e D (GEECD) (Coords. . Escalas e Testes na demência. 3ª. Lisbon: 2015.

[99] Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–72. doi:10.1192/bjp.140.6.566.

[100] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4. doi:10.1212/WNL.43.11.2412-a.

[101] Caldas AC, Garcia C, Pereira G, Fernandes L. Escalas e Testes na Demência 2007.

[102] When M. Assignment of CDR rating Clinical Dementia Rating (CDR) Scale 1993;43:2412–4.

[103] Hughes CP, Berg L, Danziger WL, Coben L a., Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–72. doi:10.1192/bjp.140.6.566.

[104] O'Bryant S. Staging Dementia Using Clinical Dementia Rating Scale Sum of Boxes Scores: A Texas Alzheimer's Research Consortium Study. Brain Behav Immun 2008;65:1091–5. doi:10.1001/archneur.65.8.1091.Staging.

[105] Reisberg B, Jamil I a., Khan S, Monteiro I, Torossian C, Ferris S, et al. Staging Dementia. Princ Pract Geriatr Psychiatry Third Ed 2010:162–9. doi:10.1002/9780470669600.ch31.

[106] Tractenberg RE, Weiner MF, Cummings JL, Patterson MB, Thal LJ. Independence of changes in behavior from cognition and function in community-dwelling persons with Alzheimer's disease: a factor analytic approach. J Neuropsychiatry Clin Neurosci

2005;17:51–60. doi:10.1176/appi.neuropsych.17.1.51.

[107] Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: A practical method for grading the state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[108] Morgado J, Rocha CS, Maruta C, Guerreiro M, Martins IP. Novos valores normativos do Mini-Mental State Examination. Sinapse 2009;9:10–6.

[109] Ousset PJ, Andrieu S, Reynish E, Puel M, Vellas B. Clinical evaluation of dementia in a cohort of 358 patients with the French version of the Clinical Dementia Rating (CDR) scale. Rev Med Interne 2003;24 Suppl 3:283s–287s.

[110] Kaufer DI, Williams CS, Braaten AJ, Gill K, Zimmerman S, Sloane PD. Cognitive Screening for Dementia and Mild Cognitive Impairment in Assisted Living: Comparison of 3 Tests. J Am Med Dir Assoc 2008;9:586–93. doi:10.1016/j.jamda.2008.05.006.

[111] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the national institute of neurological disorders and stroke-canadian stroke network vascular cognitive impairment harmonization standards neuropsychological battery after TIA and stroke. Stroke 2012;43:464–9. doi:10.1161/STROKEAHA.111.633586.

[112] Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922–35.

[113] Feldman HH, Jacova C, Robillard A, Garcia A, Chow T, Borrie M, et al. Diagnosis and treatment of dementia: 2. Diagnosis. CMAJ 2008;178:825–36. doi:10.1503/cmaj.070798.

[114] DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, et al. The Ginkgo Evaluation of Memory (GEM) study: Design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials 2006;27:238–53. doi:10.1016/j.cct.2006.02.007.

[115] Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98. doi:0022-3956(75)90026-6 [pii].

[116] Fahy S, Lawlor BA. The clock drawing test in primary care: Sensitivity in dementia detection and specificity against normal and depressed elderly. Int J Geriatr Psychiatry 2001;16:935–40. doi:10.1002/gps.445.

[117] Shulman KI, Gold DP, Cohen CA, Zucchero CA. Clock-drawing and dementia in the community: A longitudinal study. Int J Geriatr Psychiatry 1993;8:487–96. doi:10.1002/gps.930080606.

[118] Adunsky A, Fleissig Y, Levenkrohn S, Arad M, Noy S. Clock drawing task, mini-mental state examination and cognitive-functional independence measure: Relation to functional outcome of stroke patients. Arch Gerontol Geriatr 2002;35:153–60. doi:10.1016/S0167-4943(02)00018-3.

[119] Sallam K, Mostafa AMR. The use of the mini-mental state examination and the clock-drawing test for dementia in a tertiary hospital. J Clin Diagnostic Res 2013;7:484–8. doi:10.7860/JCDR/2013/4203.2803.

[120] Yamamoto S, Mogi N, Umegaki H, Suzuki Y, Ando F, Shimokata H, et al. The clock drawing test as a valid screening method for mild cognitive impairment. Dement Geriatr Cogn Disord 2004;18:172–9. doi:10.1159/000079198.

[121] Chiu YC, Li CL, Lin KN, Chiu YF, Liu HC. Sensitivity and specificity of the clock drawing test, incorporating Rouleau scoring system, as a screening instrument for questionable

and mild dementia: Scale development. Int J Nurs Stud 2008;45:75–84. doi:10.1016/j.ijnurstu.2006.09.005.

[122] Ehreke L, Luck T, Luppa M, König H-H, Villringer A, Riedel-Heller SG. Clock Drawing Test – screening utility for mild cognitive impairment according to different scoring systems: results of the Leipzig Longitudinal Study of the Aged (LEILA 75+). Int Psychogeriatrics 2011;23:1592–601. doi:10.1017/S104161021100144X.

[123] Katz S, Downs TD, Cash HR, Grotz RC. Progress in Development of the Index of ADL. Gerontologist 1970;10:20–30. doi:10.1093/geront/10.1_Part_1.20.

[124] Montejo P, Montenegro M, Fernández M a., Maestú F. Memory complaints in the elderly: Quality of life and daily living activities. A population based study. Arch Gerontol Geriatr 2012;54:298–304. doi:10.1016/j.archger.2011.05.021.

[125] Hartigan I, O'Mahony D. The Barthel Index: Comparing inter-rater reliability between Nurses and Doctors in an older adult rehabilitation unit. Appl Nurs Res 2011;24:e1–7. doi:10.1016/j.apnr.2009.11.002.

[126] Wallace M, Shelkey M. Katz Index of Independence in Activities of Daily Living (ADL). Urol Nurs Off J Am Urol Assoc Allied 2007;27:93–4. doi:10.1097/00004045-200105000-00020.

[127] Cabañero-Martínez MJ, Cabrero-García J, Richart-Martínez M, Muñoz-Mendoza CL. The Spanish versions of the Barthel index (BI) and the Katz index (KI) of activities of daily living (ADL): A structured review. Arch Gerontol Geriatr 2009;49. doi:10.1016/j.archger.2008.09.006.

[128] Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983;31:721–7.

[129] Marshall GA, Rentz DM, Frey MT, Locascio JJ, Johnson KA, Sperling RA. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement 2011;7:300–8. doi:10.1016/j.jalz.2010.04.005.

[130] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86. doi:10.1093/geront/9.3_Part_1.179.

[131] Millán-Calenti JC, Tubío J, Pita-Fernández S, González-Abraldes I, Lorenzo T, Fernández-Arruty T, et al. Prevalence of functional disability in activities of daily living (ADL), instrumental activities of daily living (IADL) and associated factors, as predictors of morbidity and mortality. Arch Gerontol Geriatr 2010;50:306–10. doi:10.1016/j.archger.2009.04.017.

[132] Monaci L, Morris RG. Neuropsychological screening performance and the association with activities of daily living and instrumental activities of daily living in dementia: Baseline and 18- to 24-month follow-up. Int J Geriatr Psychiatry 2012;27:197–204. doi:10.1002/gps.2709.

[133] Schmeidler J, Mohs RC, Aryan M. Relationship of disease severity to decline on specific cognitive and functional measures in Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:146–51. doi:10.1097/00002093-199809000-00005.

[134] Juva K, Sulkava R, Erkinjuntti T, Ylikoski R, Valvanne J, Tilvis R. Staging the severity of dementia: comparison of clinical (CDR, DSM-III-R), functional (ADL, IADL) and cognitive (MMSE) scales. Acta Neurol Scand 1994;90:293–8. doi:10.1111/j.1600-0404.1994.tb02724.x.

[135] Dillon C, Tartaglini MF, Stefani D, Salgado P, Taragano FE, Allegri RF. Geriatric

depression and its relation with cognitive impairment and dementia. Arch Gerontol Geriatr 2014. doi:10.1016/j.archger.2014.04.006.

[136] Overshott R, Burns A. Clinical assessment in dementia. Psychiatry 2007;6:491–7. doi:10.1016/j.mppsy.2007.09.007.

[137] Huang C-Q, Wang Z-R, Li Y-H, Xie Y-Z, Liu Q-X. Cognitive function and risk for depression in old age: a meta-analysis of published literature. Int Psychogeriatrics 2011;23:516–25. doi:10.1017/S1041610210000049.

[138] Blazer DG. Depression in Late Life: Review and Commentary. Journals Gerontol Ser A Biol Sci Med Sci 2003;58:M249–65. doi:10.1093/gerona/58.3.M249.

[139] Yesavage J a, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1983;17:37–49. doi:10.1016/0022-3956(82)90033-4.

[140] Alexopoulos GS. Depression in the elderly. Lancet, vol. 365, 2005, p. 1961–70. doi:10.1016/S0140-6736(05)66665-2.

[141] Allain H, Schuck S, Mauduit N. Depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;320:1287–8.

[142] Büchtemann D, Luppa M, Bramesfeld A, Riedel-Heller S. Incidence of late-life depression: a systematic review. J Affect Disord 2012;142:172–9. doi:10.1016/j.jad.2012.05.010.

[143] Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216–26. doi:10.1016/S0006-3223(03)00273-7.

[144] Mast BT, Miles T, Penninx BW, Yaffe K, Rosano C, Satterfield S, et al. Vascular Disease and Future Risk of Depressive Symptomatology in Older Adults: Findings from the Health, Aging, and Body Composition Study. Biol Psychiatry 2008;64:320–6. doi:10.1016/j.biopsych.2008.01.025.

[145] Peterson CL, Walker C, Shears G. The social context of anxiety and depression: Exploring the role of anxiety and depression in the lives of Australian adults with epilepsy. Epilepsy Behav 2014;34C:29–33. doi:10.1016/j.yebeh.2014.03.005.

[146] Belvederi Murri M, Mamberto S, Briatore L, Mazzucchelli C, Amore M, Cordera R. The interplay between diabetes, depression and affective temperaments: A structural equation model. J Affect Disord 2017;219:64–71. doi:10.1016/j.jad.2017.05.018.

[147] Cipriani G, Lucetti C, Carlesi C, Danti S, Nuti A. Depression and dementia. A review. Eur Geriatr Med 2015;6:479–86. doi:10.1016/j.eurger.2015.07.010.

[148] Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KRR, et al. Mood disorders in the medically ill: Scientific review and recommendations. Biol Psychiatry 2005;58:175–89. doi:10.1016/j.biopsych.2005.05.001.

[149] World Health Organization. Mental Health Action Plan 2013-2020. WHO Libr Cat DataLibrary Cat Data 2013:1–44.

[150] Carney RM, Freedland KE, Stein PK, Miller GE, Steinmeyer B, Rich MW, et al. Heart rate variability and markers of inflammation and coagulation in depressed patients with coronary heart disease. J Psychosom Res 2007;62:463–7. doi:10.1016/j.jpsychores.2006.12.004.

[151] Baldwin RC. Depression in Later Life. Oxford Psychiatry Libr 2014:1 online resource (119 p.). doi:10.1080/09503150601025311.

[152] Jorm AF. History of depression as a risk factor for dementia: an updated review. Aust N Z J Psychiatry 2001;35:776–81. doi:10.1046/j.1440-1614.2001.00967.x.

[153] Pocinho MTS, Farate C, Dias CA, Lee TT, Yesavage JA. Clinical and psychometric Validation of the geriatric depression scale (GDS) for portuguese elders. Clin Gerontol 2009;32:223–36. doi:10.1080/07317110802678680.

[154] Park M, Unützer J. Geriatric depression in primary care. Psychiatr Clin North Am 2011;34:469–487, ix–x. doi:10.1016/j.psc.2011.02.009.

[155] Mitchell AJ, Bird V, Rizzo M, Meader N. Diagnostic validity and added value of the Geriatric Depression Scale for depression in primary care: a meta-analysis of GDS30 and GDS15. J Affect Disord 2010;125:10–7. doi:10.1016/j.jad.2009.08.019.

[156] Prakash O, Gupta LN, Singh VB, Nagarajarao G. Applicability of 15-item Geriatric Depression Scale to detect depression in elderly medical outpatients. Asian J Psychiatr 2009;2:63–5. doi:10.1016/j.ajp.2009.04.005.

[157] Yesavage J, Sheikh J. 9/Geriatric Depression Scale (GDS) Recent Evidence and Development of a Shorter Violence. Clin Gerontol 1986;5:165–72. doi:10.1300/J018v05n01_09.

[158] Hall C a., Reynolds-III CF. Late-life depression in the primary care setting: Challenges, collaborative care, and prevention. Maturitas 2014:1–6. doi:10.1016/j.maturitas.2014.05.026.

[159] Ariza G, Blanco E, Leon M, Gonzalez-Correa JA. Polipharmacy in primary care. Eur Geriatr Med 2011;2:S-172. doi:http://dx.doi.org/10.1016/j.eurger.2011.06.002.

[160] Portuondo M, Marianao L, Urra MS, Luis J, Meliz G. Polifarmacia en el adulto mayor Polipharmacy in elders. Rev Habanera Ciencias Médicas 2013;12:142–51.

[161] Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med 1991;151:1825–32.

[162] Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003;163:2716–24. doi:10.1001/archinte.163.22.2716.

[163] Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997;157:1531–6. doi:10.1001/archinte.1997.00440350031003.

[164] Chang C Bin, Chen JH, Wen CJ, Kuo HK, Lu IS, Chiu LS, et al. Potentially inappropriate medications in geriatric outpatients with polypharmacy: Application of six sets of published explicit criteria. Br J Clin Pharmacol 2011;72:482–9. doi:10.1111/j.1365-2125.2011.04010.x.

[165] Soares M a, Fernandez-Llimos F, Lanca C, Cabrita J, Morais J a. Operacionalização para Portugal Critérios de Beers de Medicamentos Inapropriados nos Doentes Idosos. Acta Med Port 2008;21:441–52.

[166] Journal T, Geriatrics A. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2012;60:616–31. doi:10.1111/j.1532-5415.2012.03923.x.

[167] McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: A national consensus panel. CMAJ 1997;156:385–91.

[168] Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire J-P. Potentially

inappropriate prescriptions for older patients in long-term care. BMC Geriatr 2004;4:9. doi:10.1186/1471-2318-4-9.

[169] Laroche ML, Charmes JP, Merle L. Potentially inappropriate medications in the elderly: A French consensus panel list. Eur J Clin Pharmacol 2007;63:725–31. doi:10.1007/s00228-007-0324-2.

[170] Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 2008;46:72–83. doi:10.1136/ejhpharm-2012-000074.356.

[171] Ford AH. Neuropsychiatric aspects of dementia. Maturitas 2014;79:209–15. doi:10.1016/j.maturitas.2014.04.005.

[172] Delfino LL, Komatsu RS, Komatsu C, Neri AL, Cachioni M. Dementia management strategies associated with neuropsychiatric symptoms of elderly people with Alzheimer's disease. Dementia 2018. doi:10.1177/1471301218759233.

[173] G. C, C. L, C. C, S. D. Depression and dementia. A review. Eur Geriatr Med 2015;6:479–86. doi:10.1016/j.eurger.2015.07.010.

[174] Cleare A, Pariante C, Young A, Anderson I, Christmas D, Cowen P, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015;29:459–525. doi:10.1177/0269881115581093.

[175] Lotrich FEFE, Pollock BGBG. Aging and clinical pharmacology : implications for antidepressants . J Clin Pharmacol 2005;45:1106. doi:10.1177/0091270005280297.

[176] Schulz KF, Grimes D a. Epidemiology 1 - Sample size calculations in randomised trials : mandatory and mystical. Lancet 2005;365:1348–53. doi:10.1016/S0140-6736(05)61034-3.

[177] Marôco J. Analise estatistica com o SPSS Statistics. Anal. e Gest. da Inf., 2011, p. 990.

[178] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98. doi:10.1016/0022-3956(75)90026-6.

[179] Ouchi Y, Kasai M, Nakamura K, Nakatsuka M, Meguro K. Qualitative Assessment of Instrumental Activities of Daily Living in Older Persons with Very Mild Dementia: The Kurihara Project. Dement Geriatr Cogn Dis Extra 2016;6:374–81. doi:10.1159/000446769.

[180] Oliveira CR de, Rosa M santos, Anabela Mota Pinto MA, Botelho S, Morais A, Veríssimo MT. Estudo do Perfil do Envelhecimento da População Portuguesa. 2010. doi:10.3900/fpj.6.2.98.p.

[181] Direção-Geral da Saúde. Diagnóstico e Classificação da Diabetes Mellitus. Norma Da Direção Geral Da Saúde 2011:1–13.

[182] Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. J Gastrointest Liver Dis 2006. doi:5 [pii].

[183] Baber KF, Anderson J, Puzanovova M, Walker LS. Rome II versus Rome III classification of functional gastrointestinal disorders in pediatric chronic abdominal pain. J Pediatr Gastroenterol Nutr 2008. doi:10.1097/MPG.0b013e31816c4372.

[184] Marc LG, Raue PJ, Bruce ML. Screening performance of the 15-item geriatric depression scale in a diverse elderly home care population. Am J Geriatr Psychiatry 2008;16:914–

21. doi:10.1097/JGP.0b013e318186bd67.

[185] Yesavage J, Sheikh J. 9/Geriatric Depression Scale (GDS). Clin Gerontol 1986;5:165–73. doi:10.1300/J018v05n01_09.

[186] D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders: the acceptability and performance of the GDS15 and the development of shorter versions. Fam Pract 1994;11:260–6.

[187] INE. Estatísticas Demográficas. vol. 23. 2010. doi:10.1590/S1415-52732010010400001.

[188] Rosa IM, Henriques AG, Carvalho L, Oliveira J, Da Cruz E Silva OAB. Screening Younger Individuals in a Primary Care Setting Flags Putative Dementia Cases and Correlates Gastrointestinal Diseases with Poor Cognitive Performance. Dement Geriatr Cogn Disord 2017;43. doi:10.1159/000452485.

[189] Ilka M. Rosa; Ana Gabriela Henriques; Liliana Carvalho; Joana Oliveira; Odete A.B. da Cruz e Silva. Screening Younger Individuals in a Primary Care Setting Flags Putative Dementia Cases and Correlates Gastrointestinal Diseases with Poor Cognitive Performance. Dement Geriatr Cogn Disord 2016;43:15–28. doi:10.1159/000452485.

[190] Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: A narrative review. Maturitas 2014;79:196–201. doi:10.1016/j.maturitas.2014.05.008.

[191] Yasuno F, Tanimukai S, Sasaki M, Ikejima C, Yamashita F, Kodama C, et al. Effect of plasma lipids, hypertension and APOE genotype on cognitive decline. Neurobiol Aging 2012;33:2633–40. doi:10.1016/j.neurobiolaging.2011.12.028.

[192] Conejero-Goldberg C, Gomar JJ, Bobes-Bascaran T, Hyde TM, Kleinman JE, Herman MM, et al. APOE2 enhances neuroprotection against Alzheimer's disease through multiple molecular mechanisms. Mol Psychiatry 2014:1–8. doi:10.1038/mp.2013.194.

[193] Chen CH, Mizuno T, Elston R, Kariuki MM, Hall K, Unverzagt F, et al. A comparative study to screen dementia and APOE genotypes in an ageing East African population. Neurobiol Aging 2010;31:732–40. doi:10.1016/j.neurobiolaging.2008.06.014.

[194] Carvalho AC. Estatísticas Demográficas. 2013.

[195] Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 2008;7:812–26. doi:10.1016/S1474-4422(08)70169-8.

[196] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28. doi:10.1016/S1474-4422(11)70072-2.

[197] D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract 1994;11:260–6. doi:10.1093/fampra/11.3.260.

[198] Rothman KJ, Greenland S, Lash T. Modern Epidemiology. 2005. doi:10.1017/CBO9781107415324.004.

[199] Smith JD. Apolipoprotein E4: an allele associated with many diseases. Ann Med 2000;32:118–27. doi:10.3109/07853890009011761.

[200] Skoog I, Waern M, Duberstein P, Blennow K, Zetterberg H, Börjesson-Hanson A, et al. A 9-Year Prospective Population-Based Study on the Association between the APOE∗E4 Allele and Late-Life Depression in Sweden. Biol Psychiatry 2015;78:730–6. doi:10.1016/j.biopsych.2015.01.006.

[201] Rosa I., Henriques A., Carvalho L., Oliveira J. da C e SO. Screening younger individuals in a primary care setting flags putative dementia cases and correlates gastrointestinal diseases with poor cognitive performance. Dement Geriatr Cogn Disord n.d.

[202] Nagelkerke NJD. A note on a general definition of the coefficient of determination. Biometrika 1991;78:691–2. doi:10.1093/biomet/78.3.691.

[203] Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer Report 2015: The Global Impact of Dementia | Alzheimer's Disease International 2015.

[204] Gonçalves-Pereira M, Cardoso A, Verdelho A, Alves da Silva J, Caldas de Almeida M, Fernandes A, et al. Implementing a prevalence study of dementia and geriatric depression in Portugal: The 10/66 Dementia Research Group methodology. Rev Port Saude Publica 2016;34:134–43. doi:10.1016/j.rpsp.2016.03.002.

[205] Stern Y, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol 1992;32:371–5. doi:10.1002/ana.410320311.

[206] Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the Clinical Dementia Rating-Sum of Boxes as a single primary endpoint for Alzheimer's disease trials. Alzheimer's Dement 2011;7:602–10. doi:10.1016/j.jalz.2011.01.005.

[207] Fox C, Smith T, Maidment I, Hebding J, Madzima T, Cheater F, et al. The importance of detecting and managing comorbidities in people with dementia? Age Ageing 2014;43:741–3. doi:10.1093/ageing/afu101.

[208] Ravona-Springer R, Luo X, Schmeidler J, Wysocki M, Lesser G, Rapp M, et al. Diabetes is associated with increased rate of cognitive decline in questionably demented elderly. Dement Geriatr Cogn Disord 2010;29:68–74. doi:10.1159/000265552.

[209] Meneilly GS, Tessier DM. Diabetes, Dementia and Hypoglycemia. Can J Diabetes 2016. doi:10.1016/j.jcjd.2015.09.006.

[210] Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011. doi:10.1212/WNL.0b013e318227b227.

[211] Marques A, Rocha V, Pinto M, Sousa L, Figueiredo D. Comorbidities and medication intake among people with dementia living in long-term care facilities. Rev Port Saúde Pública 2015;33:42–8. doi:10.1016/j.rpsp.2014.07.005.

[212] Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JCS, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: A community-based prospective cohort study. J Am Geriatr Soc 2007. doi:10.1111/j.1532-5415.2007.01233.x.

[213] Qiu C, Winblad B, Fratiglioni L. Low diastolic pressure and risk of dementia in very old people: A longitudinal study. Dement Geriatr Cogn Disord 2009. doi:10.1159/000236913.

[214] Whitehouse-Tedd KM, Lefebvre SL, Janssens GPJ. Dietary factors associated with faecal consistency and other indicators of gastrointestinal health in the captive cheetah (Acinonyx jubatus). PLoS One 2015;10. doi:10.1371/journal.pone.0120903.

[215] Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang I a, Ukoumunne OC, et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology 2013;24:479–89. doi:10.1097/EDE.0b013e3182944410.

[216] Baptista FI, Henriques AG, Silva AMS, Wiltfang J, Da Cruz E Silva OAB. Flavonoids as

therapeutic compounds targeting key proteins involved in Alzheimer's disease. ACS Chem Neurosci 2014;5:83–92. doi:10.1021/cn400213r.

[217] Hall KE, Proctor DD, Fisher L, Rose S. American Gastroenterological Association future trends committee report: Effects of aging of the population on gastroenterology practice, education, and research. Gastroenterology 2005;129:1305–38. doi:10.1053/j.gastro.2005.06.013.

[218] Akter S, Hassan MR, Shahriar M, Akter N, Abbas MG, Bhuiyan MA. Cognitive impact after short-term exposure to different proton pump inhibitors: assessment using CANTAB software. Alzheimers Res Ther 2015;7:79. doi:10.1186/s13195-015-0164-8.

[219] Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol 2012;5:219–32. doi:10.1177/1756283X12437358.

[220] Chen M-H, Li C-T, Tsai C-F, Lin W-C, Chang W-H, Chen T-J, et al. Risk of Dementia Among Patients With Asthma: A Nationwide Longitudinal Study. J Am Med Dir Assoc 2014. doi:10.1016/j.jamda.2014.06.003.

[221] Lahousse L, Tiemeier H, Ikram MA, Brusselle GG. Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review. Respir Med 2015. doi:10.1016/j.rmed.2015.07.014.

[222] Lopez MN, Quan NM, Carvajal PM. A psychometric study of the geriatric depression scale. Eur J Psychol Assess 2010;26:55–60. doi:10.1027/1015-5759/a000008.

[223] Hölzel L, Härter M, Reese C, Kriston L. Risk factors for chronic depression - A systematic review. J Affect Disord 2011. doi:10.1016/j.jad.2010.03.025.

[224] Nöbbelin L, Bogren M, Mattisson C, Brådvik L. Risk factors for recurrence in depression in the Lundby population, 1947–1997. J Affect Disord 2018. doi:10.1016/j.jad.2017.11.038.

[225] Guelfi JD, Rousseau C, Lancrenon S. Depression and associated organic diseases: Are there any specific depressive symptoms? Results from the dialogue-2 survey. Eur Psychiatry 2004;19:446–9. doi:10.1016/j.eurpsy.2004.08.005.

[226] Bradley SM, Rumsfeld JS. Depression and cardiovascular disease. Trends Cardiovasc Med 2015;25:614–22. doi:10.1016/j.tcm.2015.02.002.

[227] Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev 2017;74:277–86. doi:10.1016/j.neubiorev.2016.07.003.

[228] Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006;27:2763–74. doi:10.1093/eurheartj/ehl338.

[229] Hamer M, Kivimaki M, Lahiri A, Marmot MG, Steptoe A. Persistent cognitive depressive symptoms are associated with coronary artery calcification. Atherosclerosis 2010;210:209–13. doi:10.1016/j.atherosclerosis.2010.01.038.

[230] Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial Aspects of the Functional Gastrointestinal Disorders. Gastroenterology 2006;130:1447–58. doi:10.1053/j.gastro.2005.11.057.

[231] Lee H-J, Lee S-Y, Kim JH, Sung I-K, Park HS, Jin CJ, et al. Depressive mood and quality of life in functional gastrointestinal disorders: differences between functional dyspepsia, irritable bowel syndrome and overlap syndrome. Gen Hosp Psychiatry 2010;32:499–

502. doi:10.1016/j.genhosppsych.2010.05.002.

[232] Aro P, Talley NJ, Ronkainen J, Storskrubb T, Vieth M, Johansson SE, et al. Anxiety Is Associated With Uninvestigated and Functional Dyspepsia (Rome III Criteria) in a Swedish Population-Based Study. Gastroenterology 2009;137:94–100. doi:10.1053/j.gastro.2009.03.039.

[233] Hein M, Lanquart J-P, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of type 2 diabetes in major depression: A study on 703 individuals referred for sleep examinations. Psychosomatics 2017. doi:10.1016/j.psym.2017.11.003.

[234] Zubenko GS, Moossy J. Major depression in primary dementia. Clinical and neuropathologic correlates. Arch Neurol 1988;45:1182–6. doi:10.1001/archneur.45.11.1182.

[235] Poletti M, Nuti A, Cipriani G, Bonuccelli U. Behavioral and psychological symptoms of dementia: Factor analysis and relationship with cognitive impairment. Eur Neurol 2013;69:76–82. doi:10.1159/000341956.

[236] Snowden MB, Atkins DC, Steinman LE, Bell JF, Bryant LL, Copeland C, et al. Longitudinal association of dementia and depression. Am J Geriatr Psychiatry 2015;23:897–905. doi:10.1016/j.jagp.2014.09.002.

[237] Fernández Martínez M, Castro Flores J, Pérez de las Heras S, Mandaluniz Lekumberri A, Gordejuela Menocal M, Zarranz Imirizaldu JJ. Risk factors for dementia in the epidemiological study of Munguialde County (Basque Country-Spain). BMC Neurol 2008;8:39. doi:10.1186/1471-2377-8-39.

[238] Bennett S, Thomas AJ. Depression and dementia: Cause, consequence or coincidence? Maturitas 2014. doi:10.1016/j.maturitas.2014.05.009.

[239] Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci 2008;10:345–57. doi:10.1016/j.bbi.2008.05.010.

[240] Sheline YI, Barch DM, Garcia K, Gersing K, Pieper C, Welsh-Bohmer K, et al. Cognitive Function in Late Life Depression: Relationships to Depression Severity, Cerebrovascular Risk Factors and Processing Speed. Biol Psychiatry 2006;60:58–65. doi:10.1016/j.biopsych.2005.09.019.

[241] Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? Am J Geriatr Psychiatry 2010;18:98–116. doi:10.1097/JGP.0b013e3181b0fa13.

[242] Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. Acta PsychiatrScand 2006;113:372–87.

[243] José Miguel Caldas de Almeida (PI) MX. Estudo epidemiológico nacional de saúde mental. 2012.

[244] Shin I-S, Carter M, Masterman D, Fairbanks L, Cummings JL. Neuropsychiatric Symptoms and Quality of Life in Alzheimer Disease. Am J Geriatr Psychiatry 2005;13:469–74. doi:10.1097/00019442-200506000-00005.

[245] Roses ADM. Apolipoprotein E Alleles as Risk Factors in Alzheimer's Disease. Annu Rev Med 1996;47:387–400. doi:10.1146/annurev.med.47.1.387.

[246] Khan TA, Shah T, Prieto D, Zhang W, Price J, Fowkes GR, et al. Apolipoprotein E genotype, cardiovascular biomarkers and risk of stroke: Systematic review and meta-analysis of 14 015 stroke cases and pooled analysis of primary biomarker data from up

to 60 883 individuals. Int J Epidemiol 2013. doi:10.1093/ije/dyt034.

[247] Darrow MD. A Practical Approach to Dementia in the Outpatient Primary Care Setting. Prim Care - Clin Off Pract 2015;42:195–204. doi:10.1016/j.pop.2015.01.008.

[248] Deneke DE, Schultz H, Fluent TE. Screening for depression in the primary care population. Prim Care 2014;41:399–420. doi:10.1016/j.pop.2014.02.011.

[249] Direção-Geral da Saúde. Abordagem Terapêutica das Alterações Cognitivas. Norma Da Direção Geral Da Saúde 2012:1–19.

[250] Nasreddine ZS, Phillips NA, B??dirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–9. doi:10.1111/j.1532-5415.2005.53221.x.

[251] Freitas S, Simões MR, Alves L, Santana I. Montreal Cognitive Assessment (MoCA): Normative study for the Portuguese population. J Clin Exp Neuropsychol 2011;33:989–96. doi:10.1080/13803395.2011.589374.

[252] Roalf DR, Moberg PJ, Xie SX, Wolk DA, Moelter ST, Arnold SE. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. Alzheimer's Dement 2013. doi:10.1016/j.jalz.2012.10.001.

[253] Beatriz Macedo Montaño Luiz Roberto Ramos MM, Roberto Ramos L. Validade da versão em português da Clinical Dementia Rating Validity of the Portuguese version of Clinical Dementia Rating. Rev Saúde Pública 2005;39:912–7. doi:10.1590/S0034-89102005000600007.

[254] Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, et al. Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease. Arch Neurol 2001;58. doi:10.1001/archneur.58.3.397.

[255] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4. doi:10.1212/WNL.43.11.2412-a.

[256] Jokanovic N, Tan ECK, Dooley MJ, Kirkpatrick CM, Bell JS. Prevalence and Factors Associated With Polypharmacy in Long-Term Care Facilities: A Systematic Review. J Am Med Dir Assoc 2015;16:535.e1-535.e12. doi:10.1016/j.jamda.2015.03.003.

[257] Samuel MJ. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–46. doi:10.1111/jgs.13702.

[258] Conejos Miquel MD, Sánchez Cuervo M, Delgado Silveira E, Sevilla Machuca I, González-Blazquez S, Montero Errasquin B, et al. Potentially inappropriate drug prescription in older subjects across health care settings. Eur Geriatr Med 2010;1:9–14. doi:10.1016/j.eurger.2009.12.002.

[259] Mann E, Böhmdorfer B, Frühwald T, Roller-Wirnsberger RE, Dovjak P, Dückelmann-Hofer C, et al. Potentially inappropriate medication in geriatric patients: The Austrian consensus panel list. Wien Klin Wochenschr 2012;124:160–9. doi:10.1007/s00508-011-0061-5.

[260] Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. Br J Clin Pharmacol 2009;68:936–47. doi:10.1111/j.1365-2125.2009.03531.x.

[261] Levy HB, Barney KF. Pharmacology, pharmacy, and the aging adult: Implications for occupational therapy. Occup. Ther. with Aging Adults Promot. Qual. Life through Collab. Pract., 2015. doi:10.1016/B978-0-323-06776-8.00022-0.

[262] Bolland B, Guignard B, Dalleur O, Lang P-O. Application of STOPP/START and Beers criteria: Compared analysis on identification and relevance of potentially inappropriate prescriptions. Eur Geriatr Med 2016:in press. doi:10.1016/j.eurger.2016.03.010.

[263] Pitkala KH, Strandberg TE, Tilvis RS. Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey. Arch Intern Med 2015;162:1707–12. doi:10.1001/archinte.162.15.1707.

[264] Gallagher P, Barry P, O'Mahony D. Inappropriate prescribing in the elderly. J Clin Pharm Ther 2007;32:113–21. doi:10.1111/j.1365-2710.2007.00793.x.

[265] Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch. Intern. Med., vol. 151, 1991, p. 1825–32.

[266] Wu C-S, Wang S-C, Chang I-S, Lin K-M. The association between dementia and long-term use of benzodiazepine in the elderly: nested case-control study using claims data. Am J Geriatr Psychiatry 2009;17:614–20. doi:10.1097/JGP.0b013e3181a65210.

[267] Wu CS, Ting TT, Wang SC, Chang IS, Lin KM. Effect of benzodiazepine discontinuation on dementia risk. Am J Geriatr Psychiatry 2011;19:151–9. doi:10.1097/JGP.0b013e3181e049ca.

[268] Elliott RA, Woodward MC, Oborne CA. Improving benzodiazepine prescribing for elderly hospital inpatients using audit and multidisciplinary feedback. Intern Med J 2001;31:529–35. doi:10.1046/j.1445-5994.2001.00139.x.

[269] Skaar DD, O'Connor HL. Use of the Beers criteria to identify potentially inappropriate drug use by community-dwelling older dental patients. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:714–21. doi:10.1016/j.oooo.2011.12.009.

[270] Bongue B, Laroche ML, Gutton S, Colvez A, Gueguen R, Moulin JJ, et al. Potentially inappropriate drug prescription in the elderly in France: a population-based study from the French National Insurance Healthcare system. Eur J Clin Pharmacol 2011;67:1291–9. doi:10.1007/s00228-011-1077-5.

[271] Fouquet A, Zegbeh H, Krolak-Salmon P, Mouchoux C. Detection of potentially inappropriate medication in a French geriatric teaching hospital: A comparison study of the French Beers criteria and the improved prescribing in the elderly tool. Eur Geriatr Med 2012;3:326–9. doi:10.1016/j.eurger.2012.07.460.

[272] Lai HY, Hwang SJ, Chen YC, Chen TJ, Lin MH, Chen LK. Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese National Health Insurance program. Clin Ther 2009;31:1859–70. doi:10.1016/j.clinthera.2009.08.023.

[273] Shaddel F, Ghazirad M, O'Leary D, Banerjee S. How psychotropic drugs are used; an explanatory paradigm. J Med Hypotheses Ideas 2015;9:S24–30. doi:10.1016/j.jmhi.2016.02.001.

[274] Weintraub D, Chen P, Ignacio R V, Mamikonyan E, Kales HC. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch Neurol 2011;68:899–904. doi:10.1001/archneurol.2011.139.

[275] Casado-Arroyo R, Gargallo C, Lanas Arbeloa ??ngel. Balancing the risk and benefits of low-dose aspirin in clinical practice. Best Pract Res Clin Gastroenterol 2012;26:173–84. doi:10.1016/j.bpg.2012.01.015.

[276] Loza E. [Systematic review: is the use of NSAIDs effective and safe in the elderly?].

Reumatol Clin 2008;4:172–82. doi:10.1016/S1699-258X(08)72461-6.

[277] Pirozzi G, Ferro G, Langellotto A, Della-Morte D, Galizia G, Gargiulo G, et al. Syncope in the elderly: An update. J Clin Gerontol Geriatr 2013;4:69–74. doi:10.1016/j.jcgg.2013.07.001.

[278] Beier MT. Updated 2012 Beers Criteria: What's Noteworthy and Cautionary? J Am Med Dir Assoc 2012;13:768–9. doi:10.1016/j.jamda.2012.08.005.

[279] Steinman MA, Rosenthal GE, Landefeld CS, Bertenthal D, Kaboli PJ. Agreement between drugs-to-avoid criteria and expert assessments of problematic prescribing. Arch Intern Med 2009;169:1326–32. doi:10.1001/archinternmed.2009.206.

[280] Steinman MA, Rosenthal GE, Landefeld CS, Bertenthal D, Sen S, Kaboli PJ. Conflicts and concordance between measures of medication prescribing quality. Med Care 2007;45:95–9. doi:10.1097/01.mlr.0000241111.11991.62.

Annexes

Annex I
Tables of the Beers Criteria

Supplementary table 1 Table I of the Beers Criteria

Table I of the Beers Criteria: 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults – PIM1 (section 1 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation.** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Anticholinergics (excludes TCAs)	**First-generation antihistamines (as single agent or as part of combination products)** Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine	**Avoid.** Highly anticholinergic; clearance reduced with advanced age. and tolerance develops when used as hypnotic; increased risk of confusion. dry mouth. constipation. and other anticholinergic effects/toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate. QE=High (Hydroxyzine and Promethazine). Moderate (All others); SR=Strong
	Antiparkinsonian agents Benztropine (oral) Trihexyphenidyl	**Avoid.** Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease. QE=Moderate; SR=Strong
	Antispasmodics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	**Avoid except in short-term palliative care to decrease oral secretions.** Highly anticholinergic. uncertain effectiveness. QE=Moderate; SR=Strong
Antithrombotic	Dipyridamole. oral short-acting* (does not apply to the extended-release combination with aspirin)	**Avoid.** May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing. QE=Moderate; SR=Strong
	Ticlopidine*	**Avoid.** Safer. effective alternatives available. QE=Moderate; SR=Strong
Anti-infective	Nitrofurantoin	**Avoid** For long-term suppression; avoid in patients with CrCl<60 mL/min. Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl<60 mL/min due to inadequate drug concentration in the urine. QE=Moderate; SR=Strong

Table I of the Beers Criteria (continued section 2 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation.** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Cardiovascular	Alpha1blockers Doxazosin Prazosin Terazosin	**Avoid use as an antihypertensive.** High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile. QE=Moderate; SR=Strong
	Alpha agonists Clonidine Guanabenz* Guanfacine* Methyldopa* Reserpine (>0.1 mg/day)*	**Avoid clonidine as a first-line antihypertensive. Avoid others as listed.** High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension. QE=Low; SR=Strong
	Antiarrhythmic drugs (Class Ia. Ic. III) Amiodarone Dofetilide Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol	**Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation.** Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults. Amiodarone is associated with multiple toxicities, including thyroid disease. pulmonary disorders. and QT interval prolongation. QE=High; SR=Strong
	Disopyramide*	**Avoid.** Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred. QE=Low; SR=Strong
	Dronedarone	**Avoid in patients with permanent atrial fibrillation or heart failure.** Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general. rate control is preferred over rhythm control for atrial fibrillation. QE=Moderate; SR=Strong
	Digoxin>0.125 mg/day	**Avoid** In heart failure. higher dosages associated with no additional benefit and may increase risk of toxicity; decreased renal clearance may increase risk of toxicity. QE=Moderate; SR=Strong
	Nifedipine. immediate release*	**Avoid.** Potential for hypotension; risk of precipitating myocardial ischemia. QE=High; SR=Strong
	Spironolactone>25 mg/day	**Avoid in patients with heart failure or with a CrCl<30 mL/min.** In heart failure. the risk of hyperkalaemia is higher in older adults if taking>25 mg/day. QE=Moderate; SR=Strong

Table I of the Beers Criteria (continued section 3 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Central Nervous System	Tertiary TCAs. alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin>6 mg/day Imipramine Perphenazine-amitriptyline Trimipramine	**Avoid** Highly anticholinergic, sedating and cause orthostatic hypotension; the safety profile of low-dose doxepin (≤6 mg/day) is comparable to that of placebo. QE=High; SR=Strong
	Antipsychotics. first(conventional) and second(atypical) generation (see online for full list)	**Avoid use for behavioural problems of dementia unless non-pharmacologic options have failed, and patient is threat to self or others** Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia. QE=Moderate; SR=Strong
	Thioridazine Mesoridazine	**Avoid** Highly anticholinergic and greater risk of QT-interval prolongation. QE=Moderate; SR=Strong
	Barbiturates Amobarbital* Butabarbital* Butalbital Mephobarbital* Pentobarbital* Phenobarbital Secobarbital*	**Avoid** High rate of physical dependence; tolerance to sleep benefits; greater risk of overdose at low dosages. QE=High; SR=Strong
	Benzodiazepines Short- and intermediate-acting: Alprazolam Estazolam Lorazepam Oxazepam Temazepam Triazolam Long-acting: Clorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	**Avoid benzodiazepines (any type) for treatment of insomnia, agitation or delirium** Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults. May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anaesthesia and end-of-life care. QE=High; SR=Strong
	Chloral hydrate*	**Avoid** Tolerance occurs within 10 days and risk outweighs the benefits considering overdose with doses only 3 times the recommended dose. QE=Low; SR=Strong

Table I of the Beers Criteria (continued section 4 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Central Nervous System	Meprobamate	**Avoid** High rate of physical dependence; very sedating. QE=Moderate; SR=Strong
	Nonbenzodiazepine hypnotics Eszopiclone Zolpidem Zaleplon	**Avoid chronic use (>90 days)** Benzodiazepine-receptor agonists that have adverse events like those of benzodiazepines in older adults (e.g. delirium. falls. fractures); minimal improvement in sleep latency and duration. QE=Moderate; SR=Strong
	Ergot mesylates* Isoxsuprine*	**Avoid** Lack of efficacy. QE=High; SR=Strong
Endocrine	Androgens Methyltestosterone* Testosterone	**Avoid unless indicated for moderate to severe hypogonadism** Potential for cardiac problems and contraindicated in men with prostate cancer. QE=Moderate; SR=Weak
	Desiccated thyroid	**Avoid** Concerns about cardiac effects; safer alternatives available. QE=Low; SR=Strong
	Oestrogens with or without progestins	**Avoid oral and topical patch. Topical vaginal cream: Acceptable to use low-dose intravaginal estrogenic for the management of dyspareunia. lower urinary tract infections. and other vaginal symptoms** Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women. Evidence that vaginal oestrogens for treatment of vaginal dryness is safe and effective in women with breast cancer. especially at dosages of oestradiol<25 mcg twice weekly. QE=High (Oral and Patch). Moderate (Topical); SR=Strong (Oral and Patch). Weak (Topical)
	Growth hormone	**Avoid. except as hormone replacement following pituitary gland removal** Effect on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia. impaired fasting glucose. QE=High; SR=Strong
	Insulin. sliding scale	**Avoid** Higher risk of hypoglycaemia without improvement in hyperglycaemia management regardless of care setting. QE=Moderate; SR=Strong

Table I of the Beers Criteria (continued section 5 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Endocrine	Megestrol	**Avoid** Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults. QE=Moderate; SR=Strong
	Sulfonylureas. long-duration Chlorpropamide Glyburide	**Avoid** Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycaemia; causes SIADH Glyburide: higher risk of severe prolonged hypoglycaemia in older adults. QE=High; SR=Strong
Gastrointestinal	Metoclopramide	**Avoid unless for gastroparesis** Can cause extrapyramidal effects including tardive dyskinesia; risk may be further increased in frail older adults. QE=Moderate; SR=Strong
	Mineral oil. given orally	**Avoid** Potential for aspiration and adverse effects; safer alternatives available. QE=Moderate; SR=Strong
	Trimethobenzamide	**Avoid** One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects. QE=Moderate; SR=Strong
Pain Medications	Meperidine	**Avoid** Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available. QE=High; SR=Strong
	Non-COX-selective NSAIDs. oral Aspirin>325 mg/day Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	**Avoid chronic use unless other alternatives are not effective, and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)** Increases risk of GI bleeding/peptic ulcer disease in high-risk groups. including those ≥75 years old or taking oral or parenteral corticosteroids. anticoagulants. or antiplatelet agents. Use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper GI ulcers. gross bleeding. or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3–6 months. and in about 2%–4% of patients treated for 1 year. These trends continue with longer duration of use. QE=Moderate; SR=Strong

Table I of the Beers Criteria (continued section 6 of 6)

	Organ System/ Therapeutic Category/Drug(s)	**Recommendation** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Pain Medications	Indomethacin Ketorolac. includes parenteral	**Avoid** Increases risk of GI bleeding/peptic ulcer disease in high-risk groups (See Non-COX selective NSAIDs) Of all the NSAIDs, indomethacin has most adverse effects. QE=Moderate (Indomethacin). High (Ketorolac); SR=Strong
	Pentazocine*	**Avoid** Opioid analgesic that causes CNS adverse effects. including confusion and hallucinations, more commonly than other narcotic drugs; is also a mixed agonist and antagonist; safer alternatives available. QE=Low; SR=Strong
	Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	**Avoid** Most muscle relaxants poorly tolerated by older adults, because of anticholinergic adverse effects. Sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults is questionable. QE=Moderate; SR=Strong
**Infrequently used drugs. Table 1 Abbreviations: ACEI-angiotensin converting-enzyme inhibitors; ARB-angiotensin receptor blockers; CNS-central nervous system; COX-cyclooxygenase; CrCl-creatinine clearance; GI-gastrointestinal; NSAIDs-non-steroidal anti-inflammatory drugs; SIADH-syndrome of inappropriate antidiuretic hormone secretion; SR-Strength of Recommendation; TCAs-tricyclic antidepressants; QE-Quality of Evidence*		

Supplementary table 2 Table II of the Beers Criteria

Table II of the 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome – PIM2 (section 1 of 4)

	Disease or Syndrome	**Drug(s)**	**Recommendation** Rationale. Quality of Evidence(QE) & Strength of Recommendation (SR)
Cardiovascular	Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (avoid only for systolic heart failure) Diltiazem Verapamil Pioglitazone. rosiglitazone Cilostazol Dronedarone	**Avoid** Potential to promote fluid retention and/or exacerbate heart failure. QE=Moderate (NSAIDs, CCBs, Dronedarone). High (Thiazolidinediones (glitazones). Low (Cilostazol); SR=Strong
	Syncope	Acetylcholinesterase inhibitors (AChEIs) Peripheral alpha blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine, thioridazine and olanzapine	**Avoid** Increases risk of orthostatic hypotension or bradycardia. QE=High (Alpha blockers). Moderate (AChEIs. TCAs and antipsychotics); SR=Strong (AChEIs and TCAs). Weak (Alpha blockers and antipsychotic).
Central Nervous System	Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	**Avoid** Lowers seizure threshold; may be acceptable in patients with well-controlled seizures in whom alter-native agents have not been effective. QE=Moderate; SR=Strong
	Delirium	All TCAs Anticholinergics Benzodiazepines Chlorpromazine Corticosteroids H2-receptor antagonist Meperidine Sedative hypnotics Thioridazine	**Avoid** Avoid in older adults with or at high risk of delirium because of inducing or worsening delirium in older adults; if discontinuing drugs used chronically, taper to avoid withdrawal symptoms. QE=Moderate; SR=Strong

Table II of the Beers Criteria (continued section 2 of 4)

	Disease or Syndrome	Drug(s)	Recommendation. Rationale. Quality of Evidence(QE) & Strength of Recommendation (SR)
Central Nervous System	Dementia & cognitive impairment Avoid.	Anticholinergics (see online for full list) Benzodiazepines H2-receptor antagonists Zolpidem Antipsychotics. chronic and as-needed use	**Avoid due to adverse CNS effects** Avoid antipsychotics for behavioural problems of dementia unless non-pharmacologic options have failed, and patient is a threat to themselves or others. Antipsychotics are associated with an increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia. QE=High; SR=Strong
	History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine hypnotics Eszopiclone Zaleplon Zolpidem TCAs/SSRIs	**Avoid unless safer alternatives are not avail able; avoid anticonvulsants except for seizure** Ability to produce ataxia. impaired psychomotor function. syncope. and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones. QE=High; SR=Strong
	Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Methylphenidate Pemoline Theobromines Theophylline Caffeine	**Avoid** CNS stimulant effects. QE=Moderate; SR=Strong
	Parkinson's disease	All antipsychotics (except for quetiapine and clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	**Avoid** Dopamine receptor antagonists with potential to worsen parkinsonian symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson disease. QE=Moderate; SR=Strong

Table II of the Beers Criteria (continued section 3 of 4)

	Disease or Syndrome	Drug(s)	Recommendation. Rationale. Quality of Evidence(QE) & Strength of Recommendation (SR)
Gastrointestinal	Chronic constipation	Oral antimuscarinics for urinary incontinence Darifenacin Fesoterodine Oxybutynin (oral) Solifenacin Tolterodine Trospium Nondihydropyridine CCB Diltiazem Verapamil First-generation antihistamines as single agent or part of combination products Brompheniramine (various) Carbinoxamine Chlorpheniramine Clemastine (various) Cyproheptadine Dexbrompheniramine Dexchlorpheniramine (various) Diphenhydramine Doxylamine Hydroxyzine Promethazine Triprolidine Anticholinergics/antispasmodics Antipsychotics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine Tertiary TCAs (amitriptyline. Clomipramine, doxepin, imipramine, and trimipramine)	**Avoid unless no other alternatives** Can worsen constipation; agents for urinary incontinence: antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops. QE=High (For Urinary Incontinence). Moderate/Low (All Others); SR=Strong
	History of gastric or duodenal ulcers	Aspirin (>325 mg/day) Non–COX-2 selective NSAIDs	**Avoid unless other alternatives are not effective, and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)** May exacerbate existing ulcers or cause new/additional ulcers. QE=Moderate; SR=Strong

Table II of the Beers Criteria (continued section 4 of 4)

	Disease or Syndrome	**Drug(s)**	**Recommendation.** Rationale. Quality of Evidence(QE) & Strength of Recommendation (SR)
Kidney/Urinary Tract	Chronic kidney disease stages IV and V	NSAIDs Triamterene(alone or in combination)	**Avoid** May increase risk of kidney injury. May increase risk of acute kidney injury. QE=Moderate (NSAIDs). Low (Triamterene); SR=Strong (NSAIDs). Weak (Triamterene)
	Urinary incontinence (all types) in women	Oestrogen oral and transdermal (excludes intravaginal estrogenic)	**Avoid in women** Aggravation of incontinence. QE=High; SR=Strong
	Lower urinary tract symptoms. benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs. except antimuscarinics for urinary incontinence.	**Avoid in men** May decrease urinary flow and cause urinary retention. QE=Moderate; SR=Strong (Inhaled agents). Weak (All others)
	Stress or mixed urinary incontinence	Alpha-blockers Doxazosin Prazosin Terazosin	**Avoid in women** Aggravation of incontinence. QE=Moderate; SR=Strong

Table 2 Abbreviations: CCBs-calcium channel blockers; AChEIs-acetylcholinesterase inhibitors; CNS-central nervous system; COX-cyclooxygenase; NSAIDs-nonsteroidal anti-inflammatory drugs; SR-Strength of Recommendation; SSRIs-selective serotonin reuptake inhibitors; TCAs-tricyclic antidepressants; QE-Quality of Evidence.

Supplementary table 3 Table III of the Beers Criteria

Table III of the Beers Criteria: 2012 AGS Beers Criteria for Potentially Inappropriate Medications to Be Used with Caution in Older Adults- PIM3

Drug(s)	**Recommendation.** Rationale. Quality of Evidence (QE) & Strength of Recommendation (SR)
Aspirin for primary prevention of cardiac events	**Use with caution in adults ≥80 years old** Lack of evidence of benefit versus risk in individuals ≥80 years old. QE=Low; SR=Weak
Dabigatran	**Use with caution in adults ≥75 years old or if CrCl<30 mL/min** Increased risk of bleeding compared with warfarin in adults ≥75 years old; lack of evidence for efficacy and safety in patients with CrCl<30 mL/min QE=Moderate; SR=Weak
Prasugrel	**Use with caution in adults ≥75 years old** Greater risk of bleeding in older adults; risk may be offset by benefit in highest risk older patients (e.g. those with prior myocardial infarction or diabetes). QE=Moderate; SR=Weak
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine SNRIs SSRIs TCAs Vincristine	**Use with caution** May exacerbate or cause SIADH or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk. QE=Moderate; SR=Strong
Vasodilators	**Use with caution** May exacerbate episodes of syncope in individuals with history of syncope. QE=Moderate; SR=Weak
Table 3 Abbreviations: CrCl-creatinine clearance; SIADH-syndrome of inappropriate antidiuretic hormone secretion; SSRIs-selective serotonin reuptake inhibitors; SNRIs-serotonin–norepinephrine reuptake inhibitors; SR-Strength of Recommendation; TCAs-tricyclic antidepressants; QE-Quality of Evidence.	

Annex II
Ethics Committee Approval

Attachments 1- Ethics Committee Approval

Ministério da Saúde

ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

Informo a proposta do projecto (remeter cópia do parecer após)
10/4/12

012804 '12 04-04 12:56

Ex.ma Senhora
Dra. Maria Fernanda Loureiro
M.I. Directora Executiva do
ACES Baixo Vouga II
Av. Dr. Lourenço Peixinho, 42/ 2ºou 6º
3800 AVEIRO

Fernanda Loureiro (Dr.ª)
Directora Executiva
ACES Baixo Vouga II

Sua referência	Sua comunicação	Nossa referência	Data
3481	7.09.11	SEC. CD	

ASSUNTO: Pedido de aprovação para a realização de um Projeto de Investigação - "Estudo Epidemiológico e Genotípico de Pacientes com Demência na Região Baixo Vouga II – Drª Ilka Martins Rosa

Para conhecimento e efeitos tidos por convenientes informa-se V. Exª que por deliberação do Conselho Diretivo foi homologado o pedido de Projeto de Investigação " Estudo Epidemiológico e Genotípico de Pacientes com Demência na Região baixo Vouga II"

Com os melhores cumprimentos

O Presidente do Conselho Directivo da ARS Centro, I.P

(Dr. José Manuel Azenha Tereso)

JT/DN

Alameda Júlio Henriques Apartado 1087 3001-553 Coimbra
Telefone 239 796 800 Fax 239 796 861 E-mail: secretariado.ca@arscentro.min-saude.pt

Annex III
Questionnaires Applied During the Clinical Interview

"Estudo Epidemiológico e Genotípico de pacientes
/Aveiro/Port

Centro de Biologia Celular
Universidade de Aveiro

CÓDIGO PACIENTE: _____ ____ ____ _____

Parte I – Critérios de Inclusão e Exclusão
Os critérios de inclusão para a amostra serão: a) Idade entre os 50 e 90 anos de idade; b) Queixa su[b]jectiva de alteração de memória. ou qualquer outra alteração da cognição confirmada por informante; c) Presença de informante capaz de fornecer dados fidedignos; Os critérios de exclusão para a amostra serão: d) Ter cancro e está em tratamento com quimioterapia ou radioterapia; e) Fazer uso de drogas ilícitas; f) Fazer uso de drogas psiquiátricas.
Parte II – Características Epidemiológicas/Sócio-Demográficas
1. Nome:_____ _____ **2. Dt.Ncto:**____/____/____ **Idade:** _____ **3. Género:** ☐ **F** ☐ **M** **4. Profissão:**_____ _____ **5. Est. Civil:** ☐Casado ☐Solteiro ☐União de Facto ☐Viúva ☐Separado **6. Com quem vive:** ☐Sozinho ☐Acompanhado **7. Se vive acompanhado. o grau de parentesco:** ☐Companheiro (a) ☐ Filho (a) ☐Irmã (o) ☐So[b]rinho (a) ☐ Pessoa contratada ☐Vive em um lar ☐Outros: _____ **8. Escolaridade:** ☐ **0-2 anos de literacia** ☐ **3-6 anos de literacia** ☐ **>7 anos de literacia** **9. Cor:** ☐ caucasiana☐ negróide ☐ asiática ☐ outra **10. Freguesia:**_____ **11. Concelho:**_____ **12. Distrito:**_____ **13. Renda Familiar Mensal:** ☐**<1 salário** ☐**1-5 salarios** ☐**5-10 salarios** ☐**>10 salários**

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Parte III– Características Clínicas
Peso :_____ Altura:_____ IMC:_____ **Glicémia: ◯ jejum ◯pós-prandial_____ Colesterol:_____**
Queixa principal:
Histórico Patológico Pregresso: ○ DM dislipidemia ○ HTA ○ Doenças do Aparelho Gastrointestinal:_____ ○ Doenças do Aparelho Respiratório: _____ ○ Doenças do Aparelho Cardiovascular: _____ ○ Doenças do Aparelho Osteoarticular: _____ ○ Doenças do Aparelho Génito-Urinário: _____ ○ Doenças Neurodegenerativas: _____ ○ Doenças Psiquiátricas:_____ ○ Doenças Hematológicas: _____ ○ Doenças Oncológicas: _____ ○ Outras: _____ ○ Etilismo
História Familiar: ○ DM ○ HTA ○ Doenças do Aparelho Gastrointestinal:_____ ○ Doenças do Aparelho Respiratório: _____ ○ Doenças do Aparelho Cardiovascular: _____ ○ Doenças do Aparelho Osteoarticular: _____ ○ Doenças do Aparelho Génito-Urinário: _____ ○ Doenças Neurodegenerativas: _____ ○ Doenças Psiquiátricas:_____ ○ Doenças Hematológicas: _____ ○ Doenças Oncológicas: _____ ○ Outras: _____

universidade de aveiro

Centro de Biologia Celular
Universidade de Aveiro

Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Uso de Medicamentos

○ **CARDIOTONICOS**	○ **ANTIARRITMICOS**	○ **ANTI-HIPERTENSORES**
○ **VASODILATADORES**	○ **VENOTRÓPICOS**	○ **ANTIDISLIPIDÉMICOS**
○ **ANTIASMÁTICOS E BRONCODILATADORES**	○ **ANTITUSSICOS E EXPECTORANTES**	○ **ANTI-ÁCIDOS E ANTI-ULCEROSOS**
○ **TTO GOTA**	○ **AINES**	○ **CORTICOIDES**
○ **TTO ARTROSE**	○ **HORMONA TIROIDE**	○ **ANSIOLITICOS**
○ **ANTIDM ORAL**	○ **INSULINA**	○ **LITIO**
○ **ANTIPSICOTICOS**	○ **ANTIDEPRESSORES**	○ **OUTROS**

Droga	Dose	Tempo de Uso	Indicação Médica

Achados sugestivos de DEMÊNCIA NÃO-ALZHEIMER (outras etiologias)

	Presente	Ausente
Alteração precoce na marcha (ataxia)		
Incontinência urinária precoce		
Flutuação na cognição: variação pronunciada na atenção e/ou alerta		
Alucinações visuais precoces. recorrentes e bem estruturadas		
Presença de parkinsonismo precoce		
Quedas de repetição		
Sensibilidade exagerada a neurolépticos		
Comportamento anti-social ou desinibição precoces		
Hiperoralidade. hiperfagia ou hipersexualidade precoces		

Centro de Biologia Celular
Universidade de Aveiro

universidade de aveiro

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Parte IV– AVALIAÇÃO COGNITIVA

1. AVALIAÇÃO CLÍNICA DA DEMÊNCIA – CDR

MEMÓRIA

1. O seu marido/A sua mulher tem problemas de memória ou de raciocínio?
   SIM ☐ NÃO ☐
   a) Se sim, estes são persistentes (constantes, contínuos)?
   SIM ☐ NÃO ☐

2. É capaz de recordar uma pequena lista? (compras...)
   Geralmente ☐ Algumas vezes ☐ Raramente ☐

3. Tem notado perda de memória no último ano?
   SIM ☐ NÃO ☐

4. É capaz de recordar acontecimentos recentes?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐

5. A perda de memória interfere com as actividades diárias que o doente era capaz de realizar há uns anos atrás)?
   SIM ☐ NÃO ☐

6. É capaz de recordar acontecimentos importantes em poucas semanas? (aniversário, viagem, visita...)
   Geralmente ☐ Algumas vezes ☐ Raramente ☐

7. É capaz de recordar pormenores desses acontecimentos?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐

8. É capaz de recordar acontecimentos importantes da sua vida passada? (data de nascimento, casamento, emprego...)
   Geralmente ☐ Algumas vezes ☐ Raramente ☐

   Conte-me algum acontecimento que tenha ocorrido recentemente (dentro do último mês), um pouco diferente do habitual (um passeio, uma visita, uma festa...) para que quando falar com o seu marido/ a sua mulher possa ficar com uma ideia sobre a sua memória. (ter atenção aos pormenores: dia, altura do dia, local, quem estava presente, o que aconteceu, etc. ...)

9. Data de Nascimento _____

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

10. Local de Nascimento _____

11. Última escola em que andou
    Nome: _____
    Local: _____
    Nível de escolaridade: _____

12. Qual foi a principal ocupação/ profissão do doente (ou cônjuge)?
    _____

13. Qual foi o último emprego (ou do cônjuge)?
    _____

14. Quando se reformou (ou cônjuge) e porquê?
    _____

ORIENTAÇÃO

1. Sabe o dia do mês
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ?[2] ☐

2. Sabe o mês
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

3. Sabe o ano
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

4. Sabe o dia da semana
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

5. Tem dificuldades com as relações temporais?
   (em situar os acontecimentos no tempo uns em relação aos outros?)
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

6. Consegue orientar-se em ruas familiares?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

7. Consegue orientar-se fora da sua área de residência?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

8. Consegue orientar-se dentro de casa?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

[2]? significa quando o cuidador não tem informações suficientes para poder responder

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

JUÍZO E RESOLUÇÂO DE PROBLEMAS

1. Como considera, actualmente, a capacidade do seu marido/da sua mulher para resolver problemas?
   - i) Como sempre ☐
   - ii) Boa, mas não tanto como anteriormente ☐
   - iii) Suficiente ☐
   - iv) Má ☐
   - v) Sem qualquer capacidade ☐

2. Qual a sua capacidade para lidar com pequenas somas de dinheiro (trocos, gorjetas...)?
   Sem defeito ☐ Defeito moderado ☐ Defeito grave ☐ ? ☐

3. Qual a capacidade para lidar com assuntos financeiros mais complexos (pagar contas, verificar livro de cheques,...)?
   Sem defeito ☐ Defeito moderado ☐ Defeito grave ☐ ? ☐

4. Como lida com um acidente em casa (pequeno incêndio, fuga de água, etc...)
   - i) Igual a antes da doença começar ☐
   - ii) Pior do que antes da doença, devido às alterações de memória ou de raciocínio ☐
   - iii) Pior do que antes da doença, devido a outras razões - quais?

   _____

5. Compreende o que se passa e aquilo que se lhe explica?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

6. Comporta-se apropriadamente nas situações sociais e na interacção com os outros?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ ? ☐

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

ACTIVIDADE NA COMUNIDADE[3]

OCUPAÇÃO

1. Ainda trabalha?
   SIM ☐ NÃO ☐ Não aplicável ☐

2. Se não, as alterações de memória interferiram na decisão de se reformar?
   SIM ☐ NÃO ☐ Não aplicável ☐

3. Se sim, tem dificuldades pelas alterações de memória ou de raciocínio?
   Geralmente ☐ Algumas vezes ☐ Raramente ☐ Não aplicável ☐

ACTIVIDADE SOCIAL

4. Alguma vez conduziu carro (ou outro veículo motorizado)?
   SIM ☐ NÃO ☐ Não aplicável ☐

   Se sim, ainda conduz?
   SIM ☐ NÃO ☐ Não aplicável ☐

   Se não conduz, é devido às alterações de memória ou de raciocínio?
   SIM ☐ NÃO ☐ Não aplicável ☐

5. Se ainda conduz há problemas ou risco por causa das alterações de memória ou de raciocínio?
   SIM ☐ NÃO ☐ Não aplicável ☐

6. É capaz, sozinho, de comprar o necessário?
   i) Raramente ou nunca - Necessita de ajuda em qualquer compra ☐
   ii) Algumas vezes - Compra algumas coisas mas traz em duplicado e esquece outras ☐
   iii) Geralmente ☐
   iv) ? ☐

7. É capaz de realizar, de forma independente, alguma actividade fora de casa?
   i) Raramente ou nunca - Necessita de ajuda em qualquer actividade ☐
   ii) Algumas vezes – Limitada e/ou de rotina ☐
   (ex. participação superficial na Igreja; ida ao cabeleireiro...)
   iii) Geralmente – Participação consciente em actividades (ex. votar) ☐
   iv) ? ☐

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

8. Tem alguma função social fora de casa e da família?
   SIM ☐ NÃO ☐
   Se não, porquê?_____

9. Um observador ocasional vê que se trata de uma pessoa doente pelo seu comportamento?
   SIM ☐ NÃO ☐ ? ☐

10. Se institucionalizado, participa em funções sociais?
    SIM ☐ NÃO ☐

ACTIVIDADES EM CASA E PASSATEMPOS[4]

1a. Tendo apenas em conta a perda cognitiva, que alterações ocorreram no desempenho das actividades domésticas?
_____

1b. Que tarefas ainda consegue realizar correctamente?
_____

2a. Tendo apenas em conta a perda cognitiva, que alterações ocorreram no desempenho dos seus passatempos?
_____

2b. Que passatempos ainda consegue realizar correctamente?
_____

3. Se institucionalizado, que actividades domésticas e passatempos ainda consegue realizar correctamente?
_____

ACTIVIDADES DO DIA-A-DIA

4. Capacidade na execução das tarefas domésticas?
   Sem defeito ☐ Defeito moderado ☐ Defeito grave ☐
   Por favor descreva-as: _____

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

5. A que nível é capaz de realizar tarefas domésticas simples e rotineiras:
   a) Sem actividade significativa ☐
   (executa actividades simples, tal como, fazer a cama com muita supervisão)
   b) Limitado a algumas tarefas simples ☐
   (com supervisão lava pratos razoavelmente bem, põe a mesa...)
   c) Independente em algumas actividades ☐
   (p. ex. manuseia aparelhos, p ex. o aspirador, a televisão; prepara refeições simples)
   d) Executa todas as tarefas, mas com algum defeito ☐
   e) Executa, como habitualmente, todas as actividades ☐

CUIDADO PESSOAL

A VESTIR
a. Normal sem ajuda ☐
b. Pequena ajuda, ocasiona/ botões mal colocados ☐
c. Sequência errada e com esquecimento de peças ☐
d. Incapaz de se vestir ☐

B HIGIENE E ARRANJO
a. Normal sem ajuda ☐
b. Tem que se chamar a atenção ☐
c. Algumas vezes necessita de ajuda ☐
d. Necessita sempre ou quase sempre de ajuda ☐

C ALIMENTAÇÃO
a. Limpo, utiliza correctamente os utensílios ☐
b. Suja tudo e utiliza apenas a colher ☐
c. Só consegue comer, sem ajuda, sólidos simples ☐
d. Tem que ser alimentado ☐

D CONTROLE ESFINCTERIANO
a. Normal, controle completo ☐
b. Urina, ocasionalmente, na cama ☐
c. Urina, frequentemente, na cama ☐
d. Totalmente incontinente ☐

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

QUESTIONÁRIO PARA O DOENTE

MEMÓRIA

1. Tem problemas de memória ou de raciocínio?
   SIM ☐ NÃO ☐

2. Há pouco o seu (marido, mulher,....) contou-me um acontecimento importante que se passou, recentemente, consigo. Quer contar-me o que aconteceu? (incentivar para que sejam referidos pormenores, tais como, datas, local, pessoas envolvidas, etc. ...) *[caso necessário, identifique qual o acontecimento].*
   Correcto ☐ Parcialmente correcto ☐ Incorrecto ☐

3. Vou dizer-lhe uma morada que quero que decore. Dentro de alguns minutos vou pedir-lhe que a diga novamente. Repita a morada depois de eu lha dizer (até um máximo de três repetições) *[assinale os elementos correctos].*
   João Silva, Rua da Fábrica, 29, Vila Real
   1 2 3 4 5
   João Silva, Rua da Fábrica, 29, Vila Real
   1 2 3 4 5
   João Silva, Rua da Fábrica, 29, Vila Real
   1 2 3 4 5
   "Óptimo, agora não se esqueça desta morada".

4. Quando nasceu _____ Correcto ☐ Incorrecto ☐

5. Onde nasceu _____ Correcto ☐ Incorrecto ☐

6. Qual foi a última escola que frequentou?
   Nome _____ Correcto ☐ Incorrecto ☐
   Local _____ Correcto ☐ Incorrecto ☐
   Nível de escolaridade _____ Correcto ☐ Incorrecto ☐

7. Repita a morada que lhe disse há pouco *[assinale os elementos correctos].*
   João Silva, Rua da Fábrica, 29, Vila Real
   1 2 3 4 5

8. Qual é/foi a sua principal profissão? (ou do cônjuge) _____
   Correcto ☐ Incorrecto ☐

9. Qual é/foi o seu último emprego? (ou do cônjuge) _____
   Correcto ☐ Incorrecto ☐

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

10. Quando é que se reformou. Porquê? (ou o cônjuge) _____

Correcto ☐ Incorrecto ☐

ORIENTAÇÃO

1. Quantos são hoje? _____ Correcto ☐ Incorrecto ☐
2. Em que mês estamos? _____ Correcto ☐ Incorrecto ☐
3. Em que ano estamos? _____ Correcto ☐ Incorrecto ☐
4. Que dia da semana é hoje? _____ Correcto ☐ Incorrecto ☐
5. Qual é o nome desta casa? _____ Correcto ☐ Incorrecto ☐
6. Em que terra estamos? _____ Correcto ☐ Incorrecto ☐
7. Sem olhar para o relógio, diga-me que horas são? (± 1 hora)
   Hora actual _____ Hora referida _____ Correcto ☐ Incorrecto ☐
8. Quem é que o acompanhou à consulta? Diga-me o nome e o parentesco.
   _____ Correcto ☐ Incorrecto ☐

JUIZO E RESOLUÇÃO DE PROBLEMAS

Se a primeira resposta do doente não merecer a pontuação máxima, insistir até compreender bem qual a capacidade do doente na compreensão do problema. Pontue a resposta mais aproximada.

SEMELHANÇAS

Se eu lhe perguntar qual a semelhança entre uma laranja e uma banana, uma resposta certa é dizer-me que são ambas frutas. Diga-me agora em que..são semelhantes (parecidos):

1. **Cão e Leão**
   - Animais, mamíferos, carnívoros (qualquer elemento abstracto) 0
   - Concreto (têm 4 patas, cauda, pelos ...) 1
   - Sem sentido ou não sabe 2
2. **Mesa e cadeira**
   - Mobília, móveis.... 0
   - Concreto (de madeira, com pés, servem para a cozinha, sala de jantar...) 1
   - Sem sentido ou não sabe 2

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

DIFERENÇAS

Se eu lhe perguntar qual a diferença entre faca e foice, uma resposta certa é dizer-me que a faca é um utensílio para cortar alimentos e a foice para cortar erva. Diga-me agora em que são diferentes:

1. **Açúcar e Vinagre**
   - P. ex. Doce e ácido ou azedo — 0
   - P. ex. Dá exemplos concretos (para pôr no café e para as saladas) — 1
   - Sem sentido ou não sabe — 2

2. **Mentira e Erro**
   - P. ex. Intencional – Não intencional — 0
   - P. ex. Só explica uma — 1
   - Sem sentido ou não sabe — 2

3. Quantas moedas de 5 cêntimos são necessárias para ter 20 cêntimos
   Correcto ☐ Incorrecto ☐

4. Quantas notas de 100 Euros são necessárias para ter 1500 Euros?
   Correcto ☐ Incorrecto ☐

5. Subtraia 3 a 30 e depois vá subtraindo 3 ao resultado obtido.
   Correcto ☐ Incorrecto ☐

CRÍTICA

6. Se chegasse a uma cidade desconhecida e quisesse entrar em contacto com um amigo que lá vivesse mas não soubesse a sua morada, como faria?
   - Consultava a lista telefónica, telefonava a um amigo comum — 0
   - Perguntava a um polícia — 1
   - Sem sentido ou não sabe — 2

7. O que faria se visse fumo a sair da janela de um seu vizinho?
   - Chamava os bombeiros, avisava as pessoas e/ou ajudava. — 2
   - Dá apenas uma alternativa correcta. — 1
   - Sem sentido ou não sabe — 0

8. Autocrítica:
   Porque veio ao médico?
   Qual é o seu estado de saúde? etc. ...(insight)
   Bom ☐ Razoável ☐ Mau ☐

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Desenho do Relógio

Pedir para desenhar um relógio redondo, colocar todas as horas e os ponteiros e marcar a hora 2:45.

Pontuação:

0 – Mau	desenho não reconhecível ou distorção grosseira
1 – Suficiente	relógio deve conter um dos seguintes: face aproximadamente circular, números de 1 a 12
2 – Bom	relógio deve conter 2 dos seguintes: face circular, números de 1 a 12, números simétricos
3 – Excelente	representação perfeita ou quase perfeita

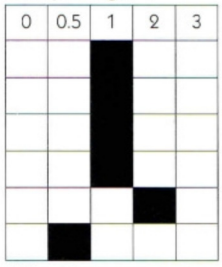
"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

AVALIAÇÃO CLÍNICA DA DEMÊNCIA

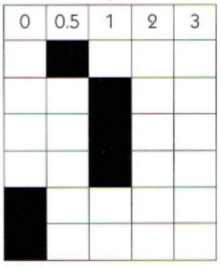
CLINICAL DEMENTIA RATING (CDR)

Exemplo regra 1



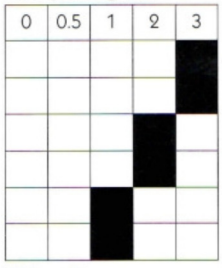
CDR = 1

Exemplo regra 4



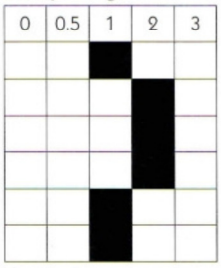
CDR = 1

Exemplo regra a



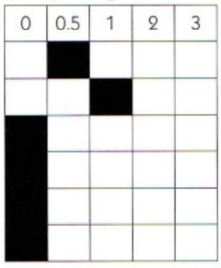
CDR = 2

Exemplo regra 2



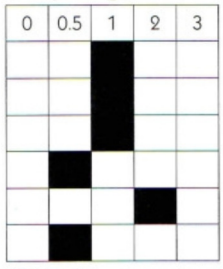
CDR = 2

Exemplo regra 5



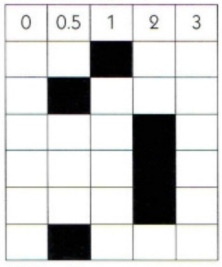
CDR = 0.5

Exemplo regra b



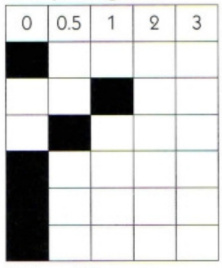
CDR = 1

Exemplo regra 3



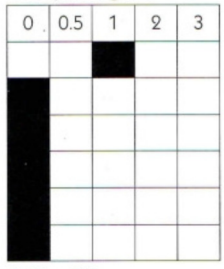
CDR = 1

Exemplo regra 6



CDR = 0.5

Exemplo regra c



CDR = 0.5

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

REGRAS

Use todas as informações disponíveis para fazer o melhor juízo possível. Pontue cada categoria (M, O, JRP, AC, CPs, Cpes) da forma mais independente possível. Pontue o grau de perda em relação ao desempenho anterior. Pontue apenas a incapacidade devida à perda cognitiva e não a incapacidade provocada por alteração motora, depressão ou perturbação da personalidade. Assinale apenas uma pontuação por categoria, sempre que existam dúvidas entre duas pontuações (p. ex. ligeira (1) ou moderada (2), escolha a que corresponde à maior incapacidade.

A afasia deve ser tida em conta tanto na avaliação das funções verbais como das não verbais em cada domínio. Se a afasia é maior do que o grau de demência, pontue de acordo com a demência global. Para isso é necessário acrescentar informações sobre funções cognitivas não verbais.

O CDR global resulta das pontuações em cada uma das seis categorias (box scores), tal como se segue.

PONTUAÇÃO

MEMÓRIA **(M)** É A CATEGORIA PRIMÁRIA, TODAS AS OUTRAS SÃO CATEGORIAS SECUNDÁRIAS **(CS)**.

1. Se pelo menos 3 **CS** são = a **M** então **CDR = M**
2. Se 3 ou + **CS** são > (ou <) a **M** então **CDR** = maioria das **CS** > (ou <) **M**
3. Sempre que 3 **CS** têm pontuação de um lado de **M** e as outras duas têm pontuações do outro lado o **CDR=M**
4. Se **M** = 0.5 e 3 ou mais **CS** são pontuadas ≥ 1 então **CDR =1**
5. Se **M** = 0.5 o **CDR** não pode ser = 0, só pode ser 0.5 ou 1
6. Se **M** = 0 então **CDR** = 0 excepto se 2 ou + **CS** forem ≥ 0.5 então **CDR** = 0.5

Embora aplicável à maioria das situações encontradas na doença de Alzheimer, estas regras não cobrem todas as combinações possíveis. Situações pouco habituais podem ocorrer na doença de Alzheimer ou surgirem noutros tipos de demências. Estas situações devem ser pontuadas da seguinte forma:

a. Quando 4 **CS** se encontram de um lado de **M**, distribuídas uniformemente por 2 pontuações, **CDR** = à pontuação mais próxima de **M** (ex. **M** e outra **CS** = 3, 2 **CS** = 2 e 2 **CS** = 1; **CDR** = 2)

b. Quando a 1 ou 2 **CS** é dada a mesma pontuação de **M**, **CDR = M**, desde que não mais de 2 **CS** estejam de um dos lados de **M**.

c. Quando **M** ≥ 1, **CDR** não pode ser = 0; nesta circunstância, **CDR** = 0.5 quando a maioria das **CS** são = 0

Nota: A CDR pode também ser cotada somando apenas o valor de cada categoria (BoxSum – Soma das caixas).

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

	NENHUMA 0	SUSPEITA 0.5	LIGEIRA 1	MODERADA 2	GRAVE 3
MEMÓRIA	Sem perda memória ou esquecimentos ligeiros e inconstantes	Esquecimentos ligeiros e consistentes; recordação parcial dos acontecimentos. Esquecimento benigno	Perda de memória moderada mais acentuada para factos recentes; o defeito interfere com as actividades do dia-a-dia	Perda grave de memória; apenas permanece o material muito aprendido; o novo material perde-se rapidamente	Grave perda de memória; só permanecem fragmentos
ORIENTAÇÃO	Bem orientado	Bem orientado com ligeira dificuldade nas relações temporais	Dificuldade moderada com as relações de tempo; orientado no espaço durante a observação; pode apresentar desorientação geográfica noutros locais	Dificuldade grave nas relações temporais; quase sempre desorientado no tempo e muitas vezes no espaço	Apenas orientado quanto à sua pessoa
JUÍZO E RESOLUÇÃO DE PROBLEMAS	Resolve bem os problemas do dia-a-dia, lida bem com os assuntos de negócios e dinheiro... O juízo crítico é bom tendo em conta o desempenho anterior	Ligeira dificuldade em resolver problemas, semelhanças e diferenças	Moderada dificuldade em resolver problemas, semelhanças e diferenças. Juízo social geralmente mantido	Dificuldade grave em resolver problemas, semelhanças e diferenças. Juízo social geralmente diminuído	Incapaz de resolver problemas ou de ter qualquer juízo crítico
ACTIVIDADES NA COMUNIDADE	Independente na sua actividade profissional habitual, compras, voluntariado e actividades sociais	Ligeira dificuldade nessas actividades	Incapaz de funcionar independentemente nessas actividades embora ainda possa desempenhar algumas; numa avaliação superficial parece normal	Sem possibilidade de um desempenho fora de casa	
CASA E PASSATEMPOS	Vida de casa e passatempos e interesses intelectuais mantidos	Vida de casa, passatempos e interesses intelectuais ligeiramente afectados	Diminuição ligeira mas evidente na realização das actividades de casa, abandono das mais complicadas; os passatempos e interesses mais complicados são também abandonados.	Só realiza as tarefas mais simples. Interesses muito limitados e pouco mantidos	Sem qualquer actividade significativa em casa
CUIDADO PESSOAL	Capacidade completa para cuidar de si próprio	Necessita de ser lembrado	Requer assistência no vestir, higiene e guarda dos objectos pessoais	Parece suficientemente bem para ser levado a actividades fora de casa	Tem um aspecto demasiado doente para poder ser levado a actividades fora de casa
					Requer muita ajuda nos cuidados pessoais. Incontinência frequente

PONTUAÇÃO GLOBAL ☐ ☐

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

1. MINI EXAME DO ESTADO MENTAL

Mini-Mental de Folstein (1975). adaptado por Brucki *et al* (2003)			
Orientação Temporal (05 pontos) *Dê um ponto para cada ítem*	Ano		
	Mês		
	Dia do mês		
	Dia da semana		
	Semestre/Hora aproximada		
Orientação Espacial (05 pontos) *Dê um ponto para cada ítem*	*País*		
	Distrito		
	Terra		
	Local geral: que local é este aqui (apontando ao redor num sentido mais amplo: hospital. casa de repouso. própria casa)		
	Andar ou local específico: em que local nós estamos (consultório.dormitório. sala. apontando para o chão)		
Retenção(3 pontos) (contar um ponto por cada palavra correctamente repetida) "Vou dizer três palavras; queria que as repetisse. mas só depois de eu as dizer todas. procure sabê-las de cor."	*Repetir:* Pêra. Gato. Bola		
Atenção e Cálculo (5 pontos) Dê 1 ponto para cada acerto. Considere a tarefa com melhor aproveitamento.	"Agora peco-lhe que me diga quantos são 30 menos 3 e depois ao número encontradovoltar a tirar 3 e repete assim ate eu dizer para parar" 30__27___24___21___18___15____		
Memória de Evocação (3 pontos)	"Veja se consegue dizer as 3 palavras que pedi a pouco para decorar"		
Nomear dois objetos (2 pontos)	Mostrar um Relógio e caneta		

Linguagem (1 ponto)	"Repita a frase que eu vou dizer: O RATO ROEU A ROLHA"		
Comando de estágios (3 pontos) Dê 1 ponto para cada ação correta)	"Apanhe esta folha de papel com a mão direita. do[b]re-a ao meio e coloque-a no chão"		
Escrever uma frase completa (1 ponto)	"Escreva alguma frase que tenha começo. meio e fim"		

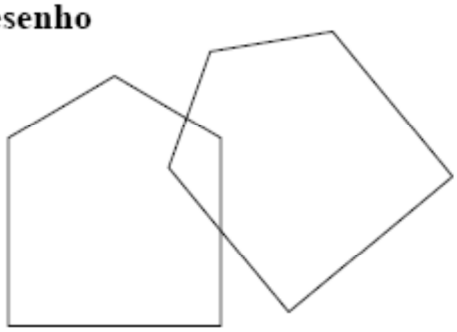
"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Ler e executar (1 ponto)	*FECHE OS OLHOS*		

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Copiar diagrama (1 ponto)	*Copiar dois pentágonos com interseção* **Desenho** 		
	PONTUAÇÃO FINAL (escore=0 a 30 pontos)		

Considera-se com defeito cognitivo:

- **22 para 0 a 2 anos de literacia**
- **24 para 3 a 6 anos de literacia**
- **27 para literacia igual ou superior a 7 anos**

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

ESCALA GERIÁTRICA DE DEPRESSÃO (Yesavage. 1983)

1. **De uma forma geral. está satisfeito (a) com a sua vida** **Sim ( ) Não ( )**
2. **Abandonou muitas das suas actividades e interesses?** **Sim ( ) Não ( )**
3. **Sente que sua vida está vazia?** **Sim ( ) Não ( )**
4. **Anda muitas vezes aborrecido(a)?** **Sim ( ) Não ( )**
5. **Está bem-disposto a maior parte do tempo?** **Sim ( ) Não ( )**
6. **Anda com medo que lhe vá acontecer alguma coisa má?** **Sim ( ) Não ( )**
7. **Sente-se feliz a maior parte do tempo?** **Sim ( ) Não ( )**
8. **Sente-se desamparado(a)?** **Sim ( ) Não ( )**
9. **Prefere ficar em casa. em vez de sair e fazer outras coisas?** **Sim ( ) Não ( )**
10. **Sente que tem mais problemas de memória do que as outras pessoas?** **Sim ( ) Não ( )**
11. **Sente que é maravilhoso estar vivo(a)?** **Sim ( ) Não ( )**
12. **Sente-se inútil nas condições actuais?** **Sim ( ) Não ( )**
13. **Sente-se cheio de energia?** **Sim ( ) Não ( )**
14. **Sente que a sua situação é desesperada?** **Sim ( ) Não ( )**
15. **Acha que a maioria das pessoas está melhor que o (a) Senhor (a)?** **Sim ( ) Não ( )**

Pontuação para GDS de 15 ítens

- **1 ponto para as respostas SIM nas questões: 2. 3. 4. 6. 8. 9. 10. 12. 14. 15**
- **1 ponto para as respostas NÃO nas questões: 1. 5. 11. 13**
- **0-5=sem depressão**
- **>5=depressão**

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

ACTIVIDADES BÁSICAS DE VIDA DIÁRIA:
(Lawton & Brody. 1969)- ÍNDICE DE KATZ

A	Independente em alimentação, continência, mobilidade, utilização do W.C., vestir-se e tomar banho	1
B	Independente para todas as funções anteriormente referidas, excepto uma	2
C	Independente para todas as funções anteriormente referidas, excepto tomar banho e outra função adicional	3
D	Independente para todas as funções anteriormente referidas, excepto tomar banho, vestir-se e outra função adicional	4
E	Independente para todas as funções anteriormente referidas, excepto tomar banho, vestir-se, utilização do W.C. e outra função adicional	5
F	Independente para todas as funções anteriormente referidas, excepto tomar banho, vestir-se, utilização do W.C, mobilidade e outra função adicional	6
G	Dependente em relação a estas seis funções	7
Outros	(dependente em, pelo menos duas funções, mas não classificável como C, D, E, ou F)	8

ATIVIDADES Pontos (1 ou 0)	INDEPENDÊNCIA (1 ponto) SEM supervisão, orientação ou assistência pessoal	DEPENDÊNCIA (0 pontos) COM supervisão, orientação ou assistência pessoal ou cuidado integral
Banhar-se; Pontos: ____	(1 ponto) Toma banho completamente ou necessita de auxílio somente para lavar uma parte do corpo como as costas, genitais ou uma extremidade incapacitada	(0 pontos) Necessita de ajuda para banhar-se em mais de uma parte do corpo, entrar e sair do chuveiro ou banheira ou requer assistência total no banho
Vestir-se; Pontos: ____	(1 ponto) Pega as roupas do armário e veste as roupas íntimas, externas e cintos. Pode receber ajuda para apertar os sapatos	(0 pontos) Necessita de ajuda para vestir-se ou necessita ser completamente vestido
Ir à casa de banho; Pontos: ____	(1 ponto) Dirige-se ao WC, entra e sai do mesmo, arruma suas próprias roupas, limpa a área genital sem ajuda	(0 pontos) Necessita de ajuda para ir ao WC, limpar-se ou usa urinol ou arrastadeira
Transferência; Pontos: ____	(1 ponto) Senta-se/deita-se e levanta-se da cama ou cadeira sem ajuda. São aceitáveis equipamentos mecânicos de ajuda	(0 pontos) Necessita de ajuda para sentar-se/deitar-se e levantar-se da cama ou cadeira
Continência; Pontos: ____	(1 ponto) Tem completo controle sobre a eliminação (intestinal ou vesical)	(0 pontos) É parcial ou totalmente incontinente a nível intestinal ou vesical
Alimentação; Pontos: ____	(1 ponto) Leva a comida do prato à boca sem ajuda. Preparação da comida pode ser feita por outra pessoa	(0 pontos) Necessita de ajuda parcial ou total com a alimentação ou requer alimentação parenteral

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

1. **ACTIVIDADE INSTRUMENTAIS DE VIDA DIÁRIA-** Pfeffer. 1982; Duarte et al. 2007.

ESCALA DE ACTIVIDADES INSTRUMENTAIS DE VIDA DIÁRIA

Escala de Lawton e Brody

Instrumental Activities of Daily Living Scale (IADL)

Lawton M.P; Brody E.M. 1969 Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 9, 179-186

A escala deve ser administrada a um acompanhante.

Não aplicável: cotar 9 (não aplicável) quando a tarefa nunca foi feita na vida. Nos casos em que a tarefa não é feita no presente por motivos aparentemente independentes da vontade ou capacidade do sujeito (ex: o sujeito não tem telefone em casa ou nunca usa os transportes públicos porque não precisa), o examinador deve formular a questão da seguinte maneira: "suponha que o doente tinha que fazer um telefonema, usar um transporte público, etc…., acha que seria capaz de o fazer?" e cotar de acordo com a resposta.

A. **Capacidade para usar o telefone**

Usa o telefone por sua iniciativa, marca os números, etc...	1
Marca alguns números mais conhecidos	2
Atende o telefone, mas não marca	3
Não usa o telefone de todo	4
Não aplicável	9

B. **Compras**

Faz todas as compras independentemente	1
Só faz, independentemente, pequenas compras	2
Necessita ser apoiado para fazer compras	3
Completamente incapaz para fazer pequenas compras	4
Não aplicável	9

C. **Cozinhar**

Planeia, prepara e serve adequadamente as refeições, de modo independente	1
Prepara as refeições adequadamente, se lhe forem dados os ingredientes	2
Aquece e serve refeições já preparadas ou prepara refeições, mas não mantem uma dieta adequada	3
Necessita que lhe preparem e sirvam as refeições	4
Não aplicável	9

D. Lida da casa

Cuida da casa sozinho ou com assistência ocasional (ex.: ajuda para trabalhos domésticos mais pesados)	1
Faz trabalhos leves, como lavar a loiça e fazer as camas	2
Faz tarefas diárias leves, mas não consegue manter um nível de limpeza aceitável	3
Necessita de ajuda em todas as tarefas domésticas	4
Não participa em qualquer actividade doméstica	5
Não aplicável	9

E. Tratamento da Roupa

Cuida completamente da lavagem da sua roupa	1
Lava pequenas peças (meias, cuecas, etc.)	2
Toda a lavagem de roupa é feita por outros	3
Não aplicável	9

F. Deslocações

Viaja independentemente em transportes públicos ou conduz o seu próprio carro	1
Desloca-se de táxi, mas não usa transportes públicos	2
Viaja em transportes públicos quando acompanhado por outras pessoas	3
Viaja, limitado a táxi ou automóvel particular com assistência de outros	4
Não viaja de todo	5
Não aplicável	9

G. Responsabilidade pelos seus próprios medicamentos

É responsável por tomar os seus medicamentos na dose e tempo correctos	1
Assume a responsabilidade, se medicação estiver separada previamente	2
Não tem capacidade para tomar conta dos medicamentos	3
Não aplicável	9

H. Capacidade para tratar das finanças

Lida com assuntos financeiros independente (orçamentos, cheques, faz pagamentos, vai ao banco)	1
Maneja o dinheiro no dia a dia, mas precisa de ajuda para lidar com somas mais avultadas	2
Incapaz de lidar com dinheiro	3
Não aplicável	9

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

As diferentes áreas que compõem a funcionalidade do idoso são conhecidas como actividades de vida diária (AVDs) e subdividem-se em:

i. Actividades Básicas de Vida Diária (ABVDs). onde estão incluídas as actividades relacionadas com o autocuidado como alimentar-se. cuidar da sua higiene pessoal. vestir-se. mobilizar-se. manter controlo dos esfíncteres;
ii. Actividades Instrumentais de Vida Diária (AIVDs). que indicam a capacidade do indivíduo ter uma vidaindependente dentro da comunidade onde vive e inclui a capacidade para preparar refeições. realizar compras. utilizartransportes. cuidar da casa. utilizar telefone. administrar as próprias finanças. tomar medicação.

- AIVDs: O Índice varia entre 8 e 30 pontos de acordo com os seguintes pontos decorte: 8 pontos – Independente; 9 a 20 pontos- Moderadamente dependente. necessita de UMA CERTA AJUDA;>20 PONTOS- SEVERAMENTE DEPENDENTE. NECESSITA DE MUITA AJUDA.

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Consentimento Informado

Por favor. leia e escreva as suas iniciais nos quadrados seguintes

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐
2. Eu percebo que a minha participação é voluntária e que sou livre de desistir. em qualquer altura. sem dar nenhuma explicação. sem que isso afecte qualquer serviço de saúde que me é prestado. ☐
3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e só os investigadores responsáveis pelo projecto da Universidade de Aveiro/Centro de Biologia Celular têm acesso a eles. E dou portanto. autorização para que os mesmos tenham acesso a esta informação. ☐
4. Eu percebo que os resultados clínicos e laboratoriais realizados durante a investigação poder ser publicadas em Jornais Científicos. usadas na própria investigação ou em outras. sem que haja qualquer quebra de confidencialidade. E dou portanto. autorização para a utilização desta informação para esses fins. ☐
5. Eu confirmo que fui esclarecida de todos os aspectos éticos da pesquisa e estou de acordo com todos eles. ☐
6. Eu concordo em participar do estudo. ☐

_____	_____	_____
Nome do Paciente	Data	Assinatura
_____	_____	_____
Nome da pessoa responsável pelo paciente	Data	Assinatura

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

Consentimento Informado

a) Folha de Informação: O pedido do Consentimento

Título do Projecto: "Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga II/Aveiro/Portugal".

Nome dos Investigadores: Odete Abreu Beirão Cruz e Silva e Ilka Martins Rosa

Informações:

- O Sr./Sra. Está convidado/a a participar num estudo de investigação clínica.
- Leia com atenção as informações abaixo. Caso as mesmas não sejam claras. ou necessitar de informação adicional. por favor pergunte aos investigadores (contacto ao fim do documento).
- Use o tempo que precisar para decidir se deseja ou não participar.
- Este projecto proporciona a garantia formal de confidencialidade e de ocultação da identidade dos participantes;
- O participante tem todo o direito de revogar o consentimento e abandonar o estudo. em qualquer altura e sem quaisquer prejuízos assistenciais ou outros;

Qual é o objectivo do estudo?

- Realizar o **"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga II/Aveiro/Portugal"**. em pacientes atendidos no Agrupamento de Saúde Baixo Vouga II;
- Realizar testes que visam testar a memória. outras funções e a capacidade em realizar tarefas do dia-a-dia;
- Realizar análises ao sangue para pesquisa de demência;

Caso eu decida participar. qual a metodologia do estudo?

- Em um primeiro momento. as pessoas entre 50-90 anos. serão convidadas a participarem do estudo.
- Será realizada recolha de dados relativamente a dados demográficos e clínicos gerais;
- Serão realizados testes de cognição reconhecidos cientificamente em três momentos. com intervalo de 01 ano cada um;
- Uma vez o paciente apresente alguma alteração dos testes de cognição. serão convidados a continuarem na pesquisa para realizarem análises ao sangue. para genotipagem e pesquisa de marcadores para Demência;

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

- Genotipagem é o estudo do conjunto de genes de uma pessoa que lhe confere as características que a mesma possui. e neste caso estamos especificamente a pesquisar se o paciente possui genes que predisponha à Doença de Alzheimer ou outras demências;
- Marcadores são substâncias que podem ser detectadas no sangue ou em outro líquido corporal. para caracterizar determinada patologia.
- A colheita sanguínea será através da punção periférica de uma veia. a ser realizada no mesmo dia da entrevista. caso o paciente cumpra os critérios e consinta.
- Não é necessário estar em jejum para a colheita de sangue.
- A recolha será realizada pela médica. Dra Ilka. Médica pesquisadora. com registo na Ordem dos Médicos de Portugal. sob número 50652;
- As análises serão realizadas no Centro de Biologia Celular. na Universidade de Aveiro. laboratório de reconhecimento europeu no Diagnóstico de Doença de Alzheimer através de Biomarcadores;
- Os resultados serão analisados estatisticamente e devidamente tratados. conforme todo o protocolo de ética exigido. com garantia da confidencialidade.

Quais os efeitos secundários de qualquer procedimento que eu vá receber quando eu participar?

- Não há efeitos secundários previsto.

Quais as desvantagens caso eu decida não participar do estudo?

- Não existe desvantagem. caso decida não participar.

Quais os possíveis benefícios. caso eu decida participar do estudo.

- Contribuir para a caracterização da população entre 50-90 anos atendida em Agrupamento de Saúde Baixo Vouga II;
- Contribuir para o rastreio de demência em Portugal;
- Possibilidade de realizar exames específicos e sensíveis e de custo inferior aos de imagem para diagnóstico de demência. nomeadamente Doença de Alzheimer;
- Enriquecer o conhecimento científico em Portugal;

Quem é que está a organizar e a financiar o estudo?

- Universidade de Aveiro- Centro de Biologia Celular
- O projecto não se responsabiliza por despesas com deslocamentos;

Contactos para mais informações sobre o estudo:

- Dra. Ilka Martins – 969299332

_____ _____ _____

Investigador Data Assinatura

"Estudo Epidemiológico e Genotípico de pacientes com Demência na Região Baixo Vouga /Aveiro/Portugal".

CÓDIGO PACIENTE: _____ **Data: ____/____/_____**

b) Declaração de consentimento pelo Paciente

Por favor. leia e escreva as suas iniciais nos quadrados seguintes

1. Eu confirmo que percebi a informação que me foi dada e tive a oportunidade de questionar e de me esclarecer. ☐
2. Eu percebo que a minha participação é voluntária e que sou livre de desistir. em qualquer altura. sem dar nenhuma explicação. sem que isso afecte qualquer serviço de saúde que me é prestado. ☐
3. Eu compreendo que os dados recolhidos durante a investigação são confidenciais e só os investigadores responsáveis pelo projecto da Universidade de Aveiro/Centro de Biologia Celular têm acesso a eles. E dou portanto. autorização para que os mesmos tenham acesso a esta informação. ☐
4. Eu percebo que os resultados clínicos e laboratoriais realizados durante a investigação poder ser publicadas em Jornais Científicos. usadas na própria investigação ou em outras. sem que haja qualquer quebra de confidencialidade. E dou portanto. autorização para a utilização desta informação para esses fins. ☐
5. Eu confirmo que fui esclarecida de todos os aspectos éticos da pesquisa e estou de acordo com todos eles. ☐
6. Eu concordo em participar do estudo. ☐

_____	_____	_____
Nome do Paciente	Data	Assinatura
_____	_____	_____
Nome da pessoa responsável pelo paciente	Data	Assinatura